

and point to our tables for demonstration. We use the old tuberculin instead of the precipitated tuberculin because it is more convenient and just as satisfactory. It has been claimed, too, that it is much more uniform in strength than the precipitated tuberculin.<sup>30</sup> Apparently slight differences in the method of preparation—for instance, in the length of time the alcohol is allowed to act on the tuberculin—give widely different results.

#### CONCLUSIONS

1. In adults the cutaneous tuberculin test is of value in diagnosis only when it is negative.

2. The frequency of its occurrence runs roughly parallel with that of the subcutaneous test.

3. The conjunctival test is of value principally on the positive side, a definite reaction indicating the presence of an active tuberculous lesion.

4. The most satisfactory results are obtained by using the two tests simultaneously. Both being negative speaks for the absence of any active tuberculous focus; both being positive, for its presence; the conjunctival negative and the cutaneous positive is no information of value.

5. We can not admit that the conjunctival or cutaneous reactions have any prognostic value.

6. The same conjunctiva should never receive a second instillation. The reaction so obtained is valueless for diagnosis and the procedure not without danger.

7. We believe that with proper precaution the conjunctival test may be used without danger of permanent injury to the eye.

8. We have been unable to confirm in any particular the claims Detre makes for his differential cutaneous reaction.

21 West Franklin Street.

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30. Hamill (S. McC.), Carpenter (H. C.) and Cope (T. A.): A comparison of the Von Pirquet, Calmette and Moro tuberculin tests and their diagnostic value. *THE ARCHIVES INT. MED.*, 1908, ii, 405. Smithies (F.) and Walker (R. E.): Diagnostic value of the cutaneous and conjunctival tuberculin reactions. *Jour. Am. Med. Assn.*, 1900, lii, 37.

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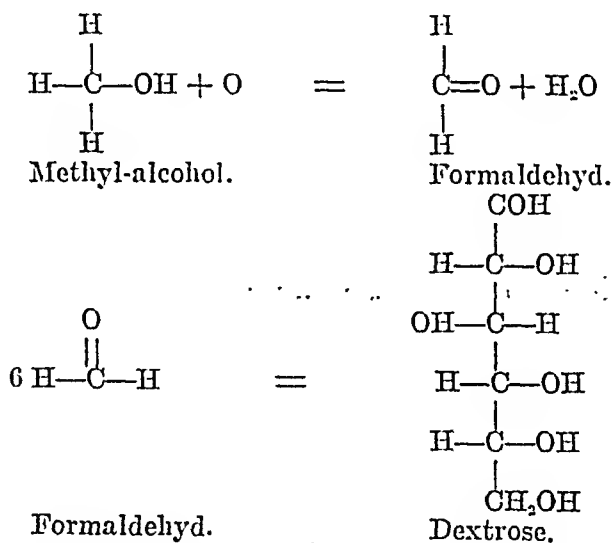
# METABOLISM IN DIABETES.\*

GRAHAM LUSK.

NEW YORK.

In my student days in Germany during the winter semester of 1898, I visited the laboratory of the botanical garden of Munich to call on Oscar Loew, who had some time before been assistant to Dr. R. Ogden Doremus in the City College of New York. Loew showed me how he was passing the vapor of methyl-alcohol ( $\text{CH}_3\text{CH}$ ) over hot oxidized wire gauze and collecting a product in water which was formaldehyd ( $\text{CH}_2\text{O}$ ). This he shook with milk of lime and obtained, after further treatment, a syrup which was as sweet as sugar and which represented the condensation of six molecules of formaldehyd into one of sugar. This artificially prepared syrup gave many reactions for sugar, but did not rotate polarized light nor was Loew able to crystallize it. At the time I had been preparing levulose in Voit's Munich laboratory. I told Loew of the difficulties of the crystallization of levulose, and that my levulose syrup would crystallize only when crystals themselves were added, and at his request I sent him some of mine. But, alas, the effort was futile. I can never forget the alternate enthusiasm and despair with which he tried to discover the hidden secret of his precious syrup. About this same time Emil Fischer showed that the substance which Loew had in his hands consisted of that kind of levulose which is optically inactive, being a mixture of right and left levulose, and Fischer indicated how levulose could be transformed into dextrose.

The changes described are according to the following formulas:



\*Lecture delivered before the Harvey Society of New York, Nov. 21, 1908.

The triumphs of pure chemistry are leading nearer and nearer to a more perfect critique of the processes underlying biologic phenomena. Long ago Baeyer suggested that the formation of sugar in the leaf was through a condensation of formaldehyd molecules into dextrose and this year Grube<sup>1</sup> has shown that formaldehyd perfused through the liver of a tortoise is converted into glycogen.

Thus the laboratory may throw a vivid light on questions of fundamental significance in the biologic world. It is from the laboratory standpoint that I wish to direct attention to the diseased condition known as diabetes. Some may question the right of a laboratory man, a physiologist, to present to medical men a scientific discussion of a diseased condition. In defense I can only quote to you the stirring words of Magendie written in Paris as long ago as 1836 as an introductory to his "Elements of Physiology," a copy of which I inherited from my father's library. Magendie said: "In a few years physiology, which is already allied with the physical sciences, will not be able to advance one particle without their aid. Physiology will acquire the same rigor of method, the same precision of language and the same exactitude of result as characterize the physical sciences. Medicine, which is nothing more than the physiology of the sick man, will not delay to follow in the same direction and to reach the same dignity. Then all those false interpretations which, as food for the weakest minds, have so long disfigured medicine, will disappear."

Let us, then, inquire into the pathologic physiology of the man sick with diabetes.

Diabetes mellitus is a condition in which the power to burn sugar within the organism is partly or completely destroyed. This condition is not to be confounded with that of glycosuria, which occurs when the sugar-holding capacity of certain organs has been reduced or overstrained.

Claude Bernard's celebrated experiment, called *la piqure*, in which he pricked certain nerve cells lying in the floor of the fourth ventricle, resulted in the appearance of sugar in the urine. Bernard named this group of cells the "diabetic center," and from this experiment has arisen the erroneous belief that diabetes is essentially of nervous origin. It has, however, been clearly demonstrated by Dock<sup>2</sup> that *la piqure* does not cause sugar excretion if the animal experimented on be fasting; that is, if the organs be free from glycogen. It is, therefore, apparent that

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1. Grube (P.): Arch. f. d. ges. Physiol., 1908, cxxi, 636.

2. Dock: Arch. f. d. ges. Physiol., 1872, v, 571.

the nerve impulses from the so-called diabetic center simply reduce the capacity for holding glycogen on the part of the liver and perhaps of other organs, with the result that the blood is flooded with sugar which is eliminated by the kidney.

Macleod and Dolley<sup>3</sup> show that after injection of nicotin, which acts to prevent the transmission of impulses through sympathetic ganglia, stimulation of the diabetic center causes neither glycosuria nor loss of liver glycogen.

The "starvation diabetes" of Hofmeister<sup>4</sup> is another example of glycosuria in which sugar ingested readily appears in the urine, because of a weakened power of the organism to retain it as glycogen. Even in normal health unlimited quantities of sugar can not be given without a portion appearing in the urine. Thus, Moritz<sup>5</sup> found 2 gm. of dextrose in the urine of a normal man who had received 200 gm. in his food. Here the dose evidently surpassed the regulatory capacity of the glyco-genic function. Moritz<sup>6</sup> also found sugar in the urine in the cases of four out of six men who had liberally partaken of carbohydrate food and champagne.

Another type of glycosuria, discovered by von Mering,<sup>7</sup> occurs after the administration of phlorhizin. There the quantity of blood sugar is reduced, since the blood coursing through the kidney has no power to retain its sugar. Hédon,<sup>8</sup> in one phlorhizinized dog, found sugar in the blood in an amount too small to determine at a time when the urine contained 11 per cent. of dextrose. Small quantities of sugar given in phlorhizin glycosuria are completely eliminated in the urine,<sup>9</sup> but if large quantities be ingested the organism is found fully able to burn sugar. Prolonged fasting does not entirely remove all the glycogen from a phlorhizinized dog,<sup>10</sup> but cold or mechanical work are able to do so.<sup>11</sup>

Von Mering and Minkowski<sup>12</sup> removed the pancreas from dogs and obtained a condition which was markedly analogous to diabetes mellitus

3. Macleod and Dolley: *Proc. Physiol. Soc., Jour. Physiol.*, 1905, xxxii, 63.

4. Hofmeister: *Arch. f. exper. Path. u. Pharmacol.*, 1890, xxvi, 355.

5. Moritz: *Verhandl. d. X Cong. f. inn. Med.*, 1891, x, 492.

6. Moritz: *Arch. f. klin. Med.*, 1890, xlvi, 217.

7. Von Mering: *Verhandl. d. V Cong. f. inn. Med.*, 1886, v, 185.

8. Hédon: *Compt. rend. Soc. biol.*, 1898, xlix, 60.

9. Reilly, Nolan and Lusk: *Am. Jour. Physiol.*, 1895, i, 395.

10. Prausnitz: *Ztschr. f. Biol.*, 1892, xxix, 168.

11. Lusk: *Am. Jour. Physiol.*, 1908, xxii, 163.

12. Von Mering and Minkowski: *Arch. f. exper. Path. u. Pharmacol.*, 1889, xxvi, 371.

in man. There is hyperglycemia and a large excretion of dextrose in the urine; ingested dextrose can not be burned, but is completely eliminated. The dogs show a considerable acidosis, with excretion of beta-oxybutyric acid, and they die in coma.<sup>13</sup> If a portion of the gland remain in the abdominal cavity there is either no diabetes or only a partial diabetes. If a portion of a pancreas be transplanted into the abdominal cavity of a depancreatized dog, the diabetes is stopped or reduced as long as the transplanted piece remains functional. Such experiments as have been made in man have not been successful. Minkowski<sup>14</sup> reports that if a piece of the pancreas be ingrafted under the skin of a dog and afterward the whole of the remainder of the pancreas be removed from the abdomen, the dog's urine remains free from sugar for two months, but on extirpation of the piece ingrafted under the skin an extreme diabetes sets in.

Minkowski<sup>15</sup> early noticed that the livers of depancreatized dogs were free from glycogen. This is further emphasized by the recent experiments of Allard,<sup>16</sup> in Minkowski's laboratory, who has shown that severe cold will not increase the sugar output in completely depancreatized dogs. The effect of cold is to produce shivering, which would convert into dextrose any available glycogen, were such within the organism.

Curiously enough, although the depancreatized dog is free from glycogen, and ingested dextrose can not be converted into glycogen, yet when levulose is given glycogen may be largely stored in the liver. The capacity for glycogen formation is, therefore, intact. It would seem, therefore, that when the cells of the organism were hungry for dextrose then an inhibition was laid on the liver, preventing its storage of glycogen from dextrose. Bang<sup>17</sup> finds no glycogen in the livers of depancreatized dogs, but finds that these same livers contain a diastatic ferment which acts energetically on a solution of glycogen. Bang and his pupils<sup>18</sup> have shown the same thing to be true in phlorhizin glycosuria.

Zuntz<sup>19</sup> removed the glycogen from a normal fasting rabbit by strychnin convulsions, and after 119 hours of further fasting found 1.3 gm. of glycogen in the liver and muscles. Hence the normal fasting organism has the power to construct glycogen. But in both pancreas

13. Allard: *Arch. f. exper. Path. und. Pharmacol.*, 1908, lix, 391.

14. Minkowski: *Arch. f. exper. Path. u. Pharmacol.*, 1908, Supplementband, 399.

15. Minkowski: *Arch. f. exper. Path. u. Pharmacol.*, 1898, xxxi, 85.

16. Allard: *Arch. f. exper. Path. u. Pharmacol.*, 1908, lix, 3.

17. Bang: *Beitr. z. chem. Physiol. u. Path.*, 1907, x, 320.

18. Bang, Ljundahl and Bohm: *Beitr. z. chem. Physiol. u. Path.*, 1907, v, 312.

19. Zuntz: *Verhandl. d. Physiol. Gesellsch. zu Berlin, Arch. f. Physiol.*, 1893, 378.

diabetes and in phlorhizin glycosuria<sup>20</sup> this power to convert dextrose into glycogen is absolutely lost.

From this discussion it is evident that when dextrose can not be burned in the organism the synthesis of glycogen from dextrose is in abeyance, whereas the reverse effect, the conversion of glycogen into sugar, is entirely normal.

The facts already noticed lead to the important conclusion that exposure to cold, which brings about an adaptive increase in heat production by greatly increasing the fat combustion, does not increase the sugar output in either pancreas or phlorhizin diabetes. Hence the sugar output is not connected with the quantity of fat metabolized. It has also been shown<sup>20</sup> that mechanical work, to accomplish which a doubled metabolism of fat would have been required, is without effect on the output of sugar in a fasting phlorhizinized dog. Seo<sup>21</sup> has made similar experiments in pancreas diabetes. When there is a partial extirpation of the gland, and, therefore, only a partial diabetes, exercise reduces the sugar output; the conditions for its oxidation are improved. But when the pancreas is completely removed, then the sugar output actually increases during the working period, to be followed by a compensatory reduction, so that in the aggregate mechanical work is entirely without influence on the sugar excretion.

From this discussion it may be safely stated that the factor of fat metabolism as increased by cold and mechanical work is without influence on the output of sugar.

The glycerin component of fat when ingested alone in diabetes is convertible into dextrose (Cremer, Lüthje). It may be that when large amounts of fat are ingested the glycerin radicle may be absorbed before the fatty acid radicle, and in that way involve a small production of sugar from fat. However, A. R. Mandel and I<sup>22</sup> have given a phlorhizinized dog 100 gm. of fat on a day when the dog actually burned only 69.5 gm. of fat, and yet there was no increase of urinary sugar. We have also<sup>23</sup> given a diabetic man 222 gm. of fat without affecting his output of sugar.

In the acute form of diabetes mellitus in man, there is complete loss of power to burn dextrose, and one may infer from the similarity of the conditions to those of pancreas diabetes that the tissues do not retain glycogen. It is evident that such an organism must exist at the expense

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20. Lusk: *Am. Jour. Physiol.*, 1908, xxii, 172.

21. Seo: *Arch. f. exper. Path. u. Pharmakol.*, 1908, lix, 341.

22. Mandel (A. R.) and Lusk: *Am. Jour. Physiol.*, 1903, x, 55.

23. Mandel and Lusk: *Deutsch. Arch. f. klin. Med.*, 1904, lxxi, 472.



of protein and fat. Within the cells of the living body, certain motions are maintained, which are manifest in such physical forms as heat, work and electricity. These material forces are not generated from nothing, but from an exact equivalent of potential energy resident in the materials burned in the body. The requirement of energy for the maintenance of the life of a man is fixed and definite and in general amounts to 32 large calories per kilogram of body substance in starvation and to 35 calories per kilogram when an average mixed diet is taken. The diabetic who can not burn dextrose is thrown on protein and fat as sources of his potential energy. Were this an uncomplicated situation a diabetic could doubtless imitate the habits of the Esquimo, who lives on oil and meat. But it happens unfortunately that a major portion of the ingested protein is convertible into sugar in the diabetic organism, and that this sugar which is carried away by the urine may contain by far the greater part of the potential energy of protein which is available for cell life. To compensate for this, the protein metabolism increases, but fat metabolism remains the mainstay of the life of the diabetic as it does in the fasting individual. In diabetes the protein metabolism is abnormal, and conditions varying in severity also arise in which the end-products of fat metabolism, such as beta-oxybutyric acid, aceto-acetic acid and acetone, do not burn, but accumulate within the organism and are eliminated in the urine.

The sugar production from protein may first be considered and later the origin of the so-called "acetone bodies." In this discussion the organism must be considered as a chemical factory working on definite materials.

Minkowski<sup>24</sup> found that, after he had extirpated the pancreas in dogs, whether they were fasting or on a meat diet, there was a constant elimination of nitrogen and dextrose in the urine and that these two substances were always in exactly the same proportion day after day. There were 2.8 gm. of dextrose for each gram of nitrogen. These two constituents rose and fell together, but their relationship, called the D:N ratio, remained constant at 2.8 to 1. Since each gram of nitrogen in the urine represents a destruction of 6.25 gm. of protein in the body, it is evident that 2.8 gm. of dextrose may arise from 6.25 gm. of protein, or protein yields 45 per cent. of dextrose.

Cremer<sup>25</sup> found that, after the frequent injection of phlorhizin, in the case of one fasting rabbit, the second day's urine gave a D:N ratio of 2.8, and he wondered if it were always so. This was repeatedly con-

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24. Minkowski: *Arch. f. exper. Path. u. Pharmacol.*, 1903, xxxi, 85.

25. Cremer and Ritter: *Ztschr. f. Biol.*, 1891, xxviii, 459.

firmed in my laboratory,<sup>26</sup> where it has also been shown that the same ratio may be obtained in phlorhizinized cats<sup>27</sup> and goats.<sup>28</sup>

The D:N ratio of 2.8 to 1, which indicated a production of 45 per cent. of sugar from protein, apparently represented the upper limit of sugar production from protein in diabetes. Minkowski's classical work did not include an experiment in which gelatin was ingested. I, therefore, tried to determine the amount of sugar which phlorhizinized rabbits would produce when gelatin was given. It became apparent that rabbits were not satisfactory animals for this kind of diet and so I began work on a dog.<sup>9</sup> During the first days the known 2.8 ratio could not be obtained, and it was fancied that this was on account of a rich sugar and glycogen supply in the dog. A continuation of the experiment on another dog showed that, even on the fifteenth day of diabetes, the 2.8 ratio appeared to be as far off as ever and that a higher ratio was constantly obtained. This higher D:N ratio was 3.65 to 1 and represented a sugar production from protein of nearly 60 per cent. Gelatin was shown to yield sugar in equal amount.

The significance of this ratio was enhanced by the discovery by Mandel and myself,<sup>23</sup> of its existence in human diabetes when the patient was placed on a diet consisting of fat and protein. Other similar cases are now on record, one of which will be discussed later.

A remarkable discovery of the present year is that of Falta,<sup>29</sup> who has shown that a D:N ratio of 3.6 to 1 may exist in dogs after removal of both pancreas and thyroid.

The cause of the variability of the ratios in different animals and in the same animal under different circumstances can not be definitely given. Falta believes that the extirpation of the thyroid and pancreas leaves the adrenal in a highly active condition, furnishing a secretion which tends to promote the formation of sugar. I do not feel that this is the place for a detailed discussion of Dr. Falta's theories regarding the interaction between the pancreas, thyroid and adrenal glands as connected with the sugar metabolism, because I have already expressed my inability to accept his views. My own views are based on the following reasoning. Loewi<sup>30</sup> has explained that the fact that blood sugar is not normally eliminated in the kidney is due to its chemical union with an unknown colloid. In diabetes mellitus sugar rises in the blood above the

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26. Lusk: *Ztschr. f. Biol.*, 1898, xxxvi, 82.

27. Arteaga: *Am. Jour. Physiol.*, 1901, vi, 175.

28. Lusk: *Ztschr. f. Biol.*, 1901, xlii, 43.

29. Eppinger, Falta and Rudinger: *Ztschr. f. klin. Med.*, 1908, lxvi, 20.

30. Loewi: *Arch. f. exper. Path. u. Pharmacol.*, 1902, xlviii, 410.

power of the colloid to unite with and the crystalloid sugar as found within the organism is readily eliminated by the kidney. In phlorhizin-diabetes, however, the secreting kidney tubules have the power to break up the colloid-dextrose combination with the reduction of blood sugar which is eliminated in the urine. Stiles and I<sup>31</sup> accepted this theory and believed that the dextrose in the colloid-dextrose radicle was not combustible, because the subcutaneous injection of 5 gm. of dextrose in a phlorhizinized dog resulted in its complete elimination in the urine. It must have been spared from combustion by its union with colloid. Mandel and I<sup>32</sup> have explained the cause of the difference between the 3.65 and 2.8 ratios by assuming the existence of two different chemical combinations, an alpha-colloid dextrose and a beta-colloid dextrose. By alpha dextrose is meant the sugar represented in the 2.8 ratio or 45 per cent. of the protein molecule. The beta-dextrose represents the additional 13.6 per cent. of the protein when the 3.65 ratio is present. The ratio would then depend on the combustion or non-combustion of the beta-colloid dextrose.

In my book on nutrition<sup>32</sup> I have called attention to the fact that in both the carbon monoxid diabetes investigated by Straub and the ether glycosuria as described by Seelig, the urinary sugar is derived exclusively from protein and may even disappear if the animal be given carbohydrates alone. This indicates the formation in protein metabolism of a distinctive chemical compound which yields dextrose. If the ether is administered with oxygen the glycosuria does not ensue. So the glycosuria is due to lack of oxygen acting on the hypothetical colloid-dextrose derived from protein. It may be that adrenalin glycosuria is of similar nature. It is certain that injections of adrenalin greatly reduce the blood supply to the tissues. Underhill and Closson<sup>33</sup> find in one experiment that the quantity of dextrose in the urine after injecting adrenalin in starvation was only slightly increased if the dog had first received 7 gm. of dextrose per kilogram. In one imperfectly described experiment Underhill states that adrenalin glycosuria is not to be prevented by free access of oxygen. Underhill believes that adrenalin stimulates sympathetic nerves causing a discharge of sugar from the glycogen repositories of the body which bring about a hyperglycemia. It seems to me, however, that to this may be rightly added a separation of dextrose from colloid-dextrose through the anemic condition of the tissues.

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31. Stiles and Lusk: *Am. Jour. Physiol.*, 1903, x, 67.

32. Lusk: *Science of Nutrition*, 1906, 234.

33. Underhill and Closson: *Am. Jour. Physiol.*, 1906, xvii, 42.

One can explain Falta's higher ratio after extirpation of both thyroid and pancreas in the dog by assuming conditions which cause the cleavage of beta-colloid dextrose.

That a molecule of protein can yield sugar to the extent of 60 per cent. of itself seems, indeed, marvelous. It is in accord with the early idea of Voit, that protein breaks up into a nitrogenous portion convertible into urica and a non-nitrogenous portion which as sugar or fat can be used by the organism. Even as late as 1902 Rubner believed in such a simple cleavage of protein which yielded large quantities of sugar, and my own papers of the same date maintained the same view.

Kossel,<sup>34</sup> however, at the International Physiological Congress, held in Cambridge, England, in 1898, first drew attention to the fact that many cleavage products of protein, such as leucin, lysin and arginin, contained six carbon atoms or the same number as dextrose, and he compared an aggregation of such amino-acids forming protein with the analogous polysaccharids. On the railway train to London after the congress, Kossel explained to me that he believed these amino-acids were convertible into dextrose and that they formed the source of urinary sugar in diabetes. The same idea was later voiced by Friedrich Müller,<sup>35</sup> who stated that protein which yielded so large a quantity of amino-acid radicles could scarcely contain a sugar radicle equal to 60 per cent. The great work of Emil Fischer has taught that the essential composition of protein is a structure formed of chains of amino-acids. He has recently hung together eighteen of these radicles in an octodecapeptid containing four leucin and fourteen glycocoll molecules and being 1-leucyl-triglycyl-1-leucyl-triglycyl-1-leucyl-octoglycyl-glycin.

$$\text{N}_2\text{NCH}(\text{C}_4\text{H}_9)\text{CO}.\text{[NHCH}_2\text{CO]}_3.\text{NHCH}(\text{C}_4\text{H}_9)\text{CO}.\text{[HNCH}_2\text{CO]}_3.\text{HNCH}(\text{C}_4\text{H}_9)\text{CO}.\text{[HNCH}_2\text{CO]}_8.\text{HNCH}_2\text{COOH}.$$

This forms a body akin to peptone. The high molecular complex called protein, which constitutes the basis of our being, is, after all, separable into simple chemical compounds. In the larger molecule these amino-acids are chained together, even as in structural framework various iron beams are riveted together. Digestive proteolysis or internal metabolism rends the higher structure of the molecule and leaves its individual supports, the amino-acids, open for further disintegration.

Kossel, Friedrich Müller and Hans Meyer were together at Marburg, and Knopf,<sup>36</sup> at Meyer's suggestion, gave an amino-acid called asparagin, commonly found in protein, to a dog which was partly under the influence of phlorhizin, and found a considerable increase of sugar

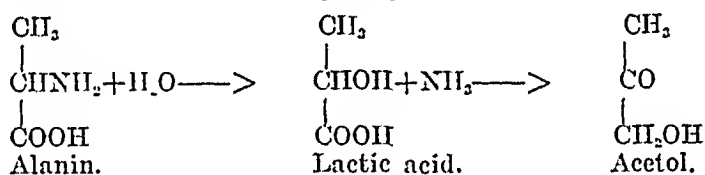
34. Kossel: Deutsch. med. Wehnsehr., 1898, xxiv, 581.

35. Müller and Seeman: Deutsch. med. Wehnsehr., 1899, xxv, 209.

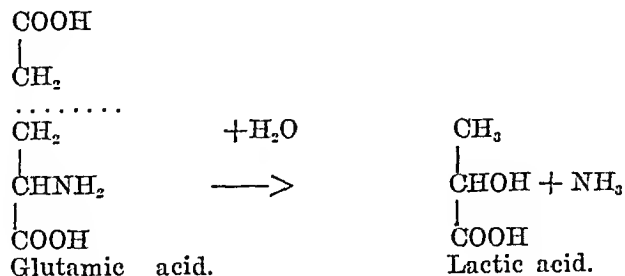
36. Knopf: Arch. f. exper. Path. und Pharmakol., 1903, xlix, 123.

in the urine. At the same time Stiles and I<sup>37</sup> fed a completely phlorhizinized dog with a pancreatic digest of meat, which had been carried so far as to contain only amino-acids. The result was a large production (40 per cent.) of sugar from the amino-acids ingested.

Embden and Salomon<sup>38</sup> have given asparagin, glycocoll and alanin to partly depancreatized dogs and have noted large increases in the amount of urinary sugar. These experiments are wanting in completeness in that the pancreas diabetes was not a total diabetes, and the same criticism is justified concerning similar experiments on phlorhizinized dogs by Baer and Blum<sup>39</sup> and Glaessner and Pick,<sup>40</sup> which have been awarded a recognition out of proportion to their worth. The true situation was first appreciated by Neuberg,<sup>41</sup> who found glycogen in the liver and lactic acid in the urine of a normal rabbit following the ingestion of alanin. The amino-acid alanin is converted into lactic acid by hydrolysis with elimination of ammonia. The ammonia is converted into urea. Arthur Mandel and I<sup>42</sup> have shown that d-lactic acid is completely converted into dextrose in the organism, and recently Ringer and I<sup>43</sup> have given 20 gm. of i-alanin to a diabetic dog and witnessed its complete elimination in the form of urinary sugar.



In the experiments published last June, I<sup>44</sup> showed the probability that glutamic acid was convertible into sugar in so far as it could form alanin in the organism. This would take place according to the following reaction:



37. Stiles and Lusk: *Am. Jour. Physiol.*, 1903, ix, 380.

38. Embden and Salomon: *Beitr. z. chem. Physiol. u. Path.*, 1904, v, 507; vi, 63.

39. Baer and Blum: *Beitr. z. chem. Physiol. u. Path.*, 1908, ii, 101.

40. Glaessner and Pick: *Beitr. z. chem. Physiol. u. Path.*, 1908, 473.

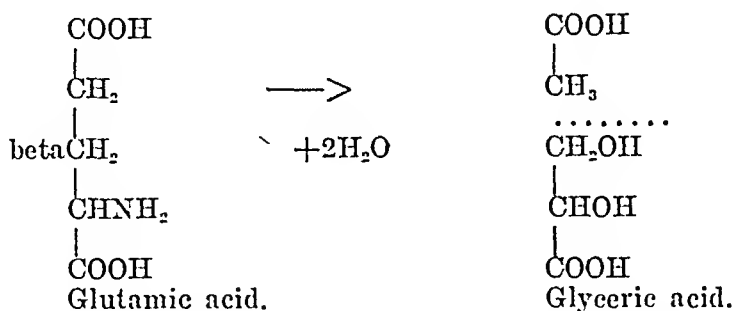
41. Neuberg and Langstein: *Arch. f. Physiol.*, 1903, Supplementband, 514.

42. Mandel and Lusk: *Am. Jour. Physiol.*, 1906, xvi, 129.

43. Unpublished.

44. Lusk: *Am. Jour. Physiol.*, 1908, xxii, 174.

Or it may be that the cleavage of the glutamic acid may be brought about by hydrolysis of the beta-carbon with the production of glyceric acid as follows:



The glyceric acid would then be converted into dextrose.

This method of giving individual amino-acids in diabetes is entirely sufficient to yield information regarding the quantity of sugar production from glycocoll, aspartic acid, serin and other characteristic building-stones of protein.

On closer consideration it appears remarkable that i-alanin, which is composed of d-alanin found in protein and l-alanin which is only an artificial product, should be completely converted into dextrose. The right-handed and left-handed lactic acid must be equally convertible into dextrose. By what chemical process this synthesis of glucose from i-lactic acid is accomplished is difficult to conjecture. That it should be built up immediately through methylglyoxal and glycerin aldehyd, according to the scheme of Wohl,<sup>45</sup> seems difficult to imagine. Certainly the lactic acid can not break up into carbonic acid and alcohol, according to the idea of Sloklasa and Büchner, for these substances do not form dextrose within the organism. On the other hand, if the lactic acid is converted into acetol,  $\text{CH}_3\text{—CO—CH}_2\text{OH}$ , and finally into formaldehyd, according to the teachings of Walter Löb,<sup>46</sup> the formation of dextrose from the broken fragments would be in accord with modern knowledge. For we have seen that the liver can build glycogen from formaldehyd. One might imagine that this line of varying transformation would be at the sacrifice of some of the potential energy resident in alanin.

Rubner<sup>47</sup> has shown that 28.5 per cent. of the heat value of protein is never utilized by the cells to give them their required energy, but it is lost to the body as waste heat. This power of protein to yield free heat Rubner termed the specific dynamic action of protein. Fats and starches exert a much smaller specific dynamic action because there is only slight

45. Wohl: *Biochem. Ztschr.*, 1907, v, 45.

46. Löb: *Biochem. Ztschr.*, 1908, xii, 85.

47. Rubner: *Gesetze des Energieverbrauchs*, 1902.

heat loss in their conversion into compounds which are directly metabolizable by the cells.

It is on account of this free heat liberated from the different food-stuffs, heat which can not contribute to the necessary mechanics of cell life, that the heat production after food ingestion is greater than during fasting. Rubner conceives the actual energy requirement of the cells to be ever constant under wide variations in the food supply, and this energy must be furnished to the cells in directly metabolizable compounds. No heat is set free when protein molecules break up into amino-acids,<sup>48</sup> and amino-acids themselves possess the same specific dynamic action as protein.<sup>49</sup> Some heat, however, is liberated when amino-acids are hydrolized to oxy-acids.<sup>50</sup> If one gram of lactic acid containing 3,661 calories were directly converted into one gram of dextrose containing 3,755 calories, there would be little change in the heat relations. If, however, lactic acid was first broken down into formaldehyd and then synthesized into dextrose before it could be used by the cells, energy changes might ensue. However, one gram of formic aldehyd yields 4,010 calories.<sup>51</sup> Hence the energy changes in this intermediate metabolism would be inconsiderable and would not explain the cause of the specific dynamic action of protein.

When one considers that protein in its metabolism yields 28.5 per cent. of its energy content as free heat, and that, besides this, the diabetic eliminates 52.5 per cent. of its energy in the form of urinary sugar, it is evident that the physiologic heat value of protein to the organism in diabetes is only 19 per cent., or its usually calculated value. As if to compensate for this, the protein metabolism rises threefold to fivefold after the administration of phlorhizin to fasting dogs, and Falta<sup>52</sup> has found almost as great a rise in dogs after extirpation of the pancreas. Falta<sup>53</sup> also states that he does not find a higher protein metabolism in human diabetes than normal. Mandel and I, however, in a study of an individual in whom there was complete intolerance for carbohydrates, found that the greatly emaciated patient, when put on a diet containing 7 gm. of nitrogen, still lost 14 gm. of body nitrogen besides, an amount which we considered high under the circumstances.

Allard<sup>54</sup> reports a case of a greatly emaciated diabetic man who during fasting excreted between 13 and 14 gm. of nitrogen in the urine

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48. Grafe: *Arch. f. Hyg.*, 1907, lxii, 216.

49. Falta, Grote and Staehelin: *Beitr. z. chem. Physiol. u. Path.*, 1907, ix, 372.

50. Rubner: *Arch. f. Hyg.*, 1908, lxvi, 1.

51. Landolt and Bornstein: *Physikalisch-chemische Tabelle*.

52. Falta, Grote and Staehelin: *Beitr. z. chem. Physiol. u. Path.*, 1907, x, 199.

53. Falta: *Berl. klin. Wchnschr.*, 1908, xlv, 51.

54. Allard: *Arch. f. exper. Path. u. Pharmakol.*, 1907, lvii, 1.

daily. This certainly seems a large amount, considering the condition of the patient.

The total energy requirement of a diabetic is not far different from that of a normal man. Thus, E. Voit<sup>55</sup> calculated that the heat production of the diabetic patient experimented on by Pettenkofer and Voit in 1867 amounted to 1,015 calories per square meter of surface as compared with 1,020 calories for a normal individual of similar size. It seems astonishing that a single experiment of Pettenkofer and Voit should have remained for more than forty years a solitary instance of a complete record of the respiratory metabolism in diabetes.

Magnus-Levy,<sup>56</sup> from experiments made on diabetics with the Zuntz respiration apparatus, which determines the respiratory exchange of an individual during a brief interval of time, comes to the conclusion that the total metabolism may be slightly increased in severe diabetes. In phlorhizin glycosuria Mandel and I<sup>57</sup> have shown little or no change in the total heat production from the normal.

Rubner,<sup>58</sup> however, finds that the total metabolism of a dog kept constantly in an environmental temperature of 33 degrees rises from 478 calories on normal fasting days to 510 calories on the days of phlorhizin glycosuria. This 7 per cent. increase in heat production he ascribes to the specific dynamic action of the increased protein metabolism. In this experiment, as in all my own, the fat metabolism remained almost unchanged from the normal, whereas the protein metabolism rose to compensate for the loss of calories eliminated in the urinary sugar.

Sharply discordant with these results are those of Falta, Grote and Staehelin<sup>59</sup> on depancreatized dogs. In one dog these authors noticed a rise in heat production after extirpation of the pancreas to from 33 to 54 per cent. of the normal amount. But the dog had a small abscess and his temperature ran between 39.4 and 40 degrees after the operation as contrasted with a normal of 38.3 degrees before the operation. In a second dog, abscesses were also found on autopsy, and during one day when the body temperature ran from 38.8 to 39.9 degrees there was an increased heat production of 88 per cent. above the normal, and then during a single three-hour morning period, when the body temperature was low (38.7 to 38.5 degrees), the total metabolism was only 42 per cent. above the normal. This experiment shows the tremendous influence of a fall

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55. Lusk: *Ztschr. f. Biol.*, 1890, xxvii, 478.

56. Magnus-Levy: *Ztschr. f. klin. Med.*, 1905, lvi, 83.

57. Mandel and Lusk: *Am. Jour. Physiol.*, 1903, x, 47.

58. Rubner: *Gesetze des Energieverbrauchs*, 1902, 370.

59. Falta, Grote and Staehelin: *Beitr. z. chem. Physiol. u. Path.*, 1907, x, 1.



in body temperature on metabolism, but it does not show that the morning metabolism of a diabetic dog which had had a temperature of 39.9 the night before is to be considered an uncomplicated criterion of metabolism in diabetes. There might have been an overheating of the cells where metabolism was progressing, even though this was not determinable by the clinical thermometer—an explanation offered by Rubner to explain the rise in metabolism of a fat man in warm air when there was no observable change in his body temperature. From the knowledge at hand the foundations of a diet for a diabetic should, therefore, be one containing about the normal quantity of calories or 35 calories per kilogram of body weight.

Rosenfeld<sup>60</sup> has pointed out that there is a distinct antagonism between glycogen and fat deposit in the liver. In fasting the quantity of fat in the liver may increase and the fat in the blood also increases. The body fat is transported from its normal repositories in order to feed the tissues. In pancreas diabetes and in phlorhizin glycosuria this condition is intensified so that 40 and even 50 per cent. of the liver solids may consist of fat. Klemperer and Umber<sup>61</sup> have recently reported that of nine persons with diabetes with acidosis seven had lipemia. Ewing,<sup>62</sup> citing his own work and that of others, finds that the livers of diabetics when they come to autopsy are not fatty in character. This may, perhaps, be explained by the fact that in human diabetics there is rarely a complete loss of power to burn carbohydrate. I have the record of a patient who, revived from coma on administration of bicarbonate of soda, was able to burn ingested carbohydrate in small amount three weeks later without the appearance of any sugar in the urine.

The pre-eminence of fat metabolism in the diabetic as the mainstay of his organism leads to inquiry as to the origin of the fatty acid called beta-oxybutyric acid, and aceto-acetic acid and acetone which are directly derived from it. Whence do these acetone bodies arise? They were at first supposed to come from dextrose, following a chemical process analogous to the butyric acid fermentation of carbohydrates, but it was soon discovered that in normal persons the acetone bodies were especially found in the fasting state. Many then attributed the presence of acetone to the specific breakdown of body protein, since, when protein was given in the food, the acetone bodies disappeared in the urine. However, Magnus-Levy<sup>63</sup> has reported a case of a boy in coma who eliminated an

60. Rosenfeld: *Ergebnisse der Physiologie*, 1903, ii, 50.

61. Klemperer and Umber: *Ztschr. f. klin. Med.*, 1908, lxxv, 340.

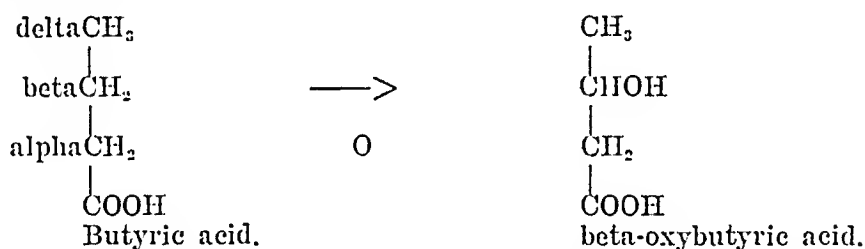
62. Ewing (James): *Acidosis and Associated Conditions*, *Arch. Int. Med.*, 1908, ii, 330.

63. Magnus-Levy: *Ergebn. d. inn. Med.*, 1908, i, 374.

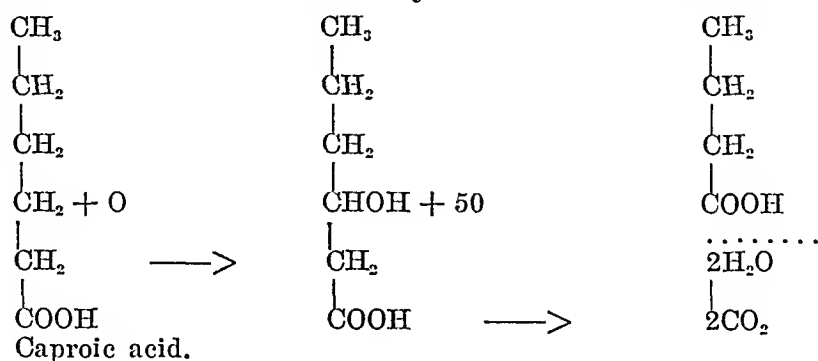
average of 97.5 gm. of beta-oxybutyric acid and aceto-acetic acid daily for three days in addition to an unmeasured quantity of acetone in the breath, and during this time the protein metabolism amounted to 90 gm., of which latter at least 40 gm. appeared as sugar in the urine. The 97.5 gm. of acetone bodies in this case could not have been entirely derived from the 90 gm. of protein, but they must have originated from fat.

Stadelman<sup>64</sup> first pointed out the relationship between the formation of beta-oxybutyric acid and the occurrence of coma. Coma has been compared to the sword of Damocles which hangs suspended over every diabetic. It has been discovered that whenever the organism is thrown suddenly from a carbohydrate regimen to a combustion of fat the acetone bodies appear in the urine. This condition is greatly intensified in diabetes when even the sugar derived from protein is not burned.

Knoop,<sup>65</sup> through cleverly devised experiments, has shown that the oxidation of fatty acids in the body is effected by an attack on the fatty molecule at the carbon in the beta-position. Thus, the first step in the metabolism of butyric acid would be the oxidation of its beta-carbon atom as follows:



In a similar manner, caproic acid would first be oxidized at its beta-carbon atom and then on further oxidation would lose two atoms of carbon and be converted into butyric acid, which, in turn, becomes beta-oxybutyric acid. These reactions may be written as follows:



64. Stadelman: Experimentell-klinische Untersuchungen, Stuttgart, 1890.

65. Knoop: Beitr. z. chem. Physiol. u. Path., 1904, vi, 150.

Such, indeed, is believed to be the method of successive oxidation of all the fatty acids, of palmitic acid  $C_{16}H_{32}O_2$ , of oleic acid  $C_{18}H_{34}O_2$ , of stearic acid  $C_{18}H_{36}O_2$ . It is evident that each successive oxidation carries away two carbon atoms and that beta-oxybutyric acid can be produced only from fatty acids having an even number of carbon atoms. Valerianic acid, for example, with five atoms of carbon, can not yield beta-oxybutyric acid. The organism has an apparent preference for fats with an even number of carbon atoms, and each of these fatty acids on their way in metabolism yields a molecule of beta-oxybutyric acid.

Each molecule of butyric acid can yield one of beta-oxybutyric acid. It has been calculated by Magnus-Levy<sup>66</sup> that 100 gm. of neutral fat made of stearin, palmitin and olein may yield 36.2 gm. of beta-oxybutyric acid. It is, therefore, evident that the higher fatty acids are the more valuable nutriment. Butter, with its high content of butyric acid, largely increases the output of the acetone bodies in diabetes. Fifty to 100 gm. of butter fat when administered to a diabetic may raise his acetone output four to eightfold.<sup>67</sup> Oleomargarin is to be preferred.

Joslin<sup>68</sup> has shown that oleic acid yields acetone more readily in diabetes than do palmitic and stearic acids.

The story of the formation of beta-oxybutyric acid does not end with the metabolism of fat, for many of the amino-acids of protein yield this acid in metabolism. From the experiments of Embden, Salomon and Schmidt,<sup>69</sup> Baer and Blum,<sup>70</sup> it has been discovered that leucin may yield beta-oxybutyric acid, whereas amino-butyric and normal aminocaproic acids do not. Friedrich Müller, in his Hertter lectures two years ago, mentioned the fact that he had administered amino-valerianic acid to a diabetic patient, with resulting increase in the beta-oxybutyric acid excretion.

These statements are all conformant with the idea of a beta-oxidation of fatty molecules. Thus, when alpha-amino-valerianic acid, one of the building-stones of protein, is ingested, it undergoes hydrolysis in the intestinal wall and loses ammonia. Its further oxidation results in the production of butyric acid, which is now oxidized on the beta-carbon. The reaction is as follows:

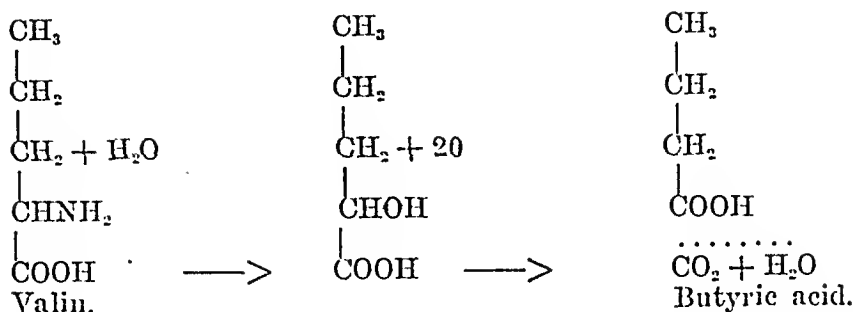
66. Magnus-Levy: *Ergebn. d. inn. Med.*, 1908, i, 384.

67. Fejes: *Magyar orvosi Archivum*, 1907, viii, 335.

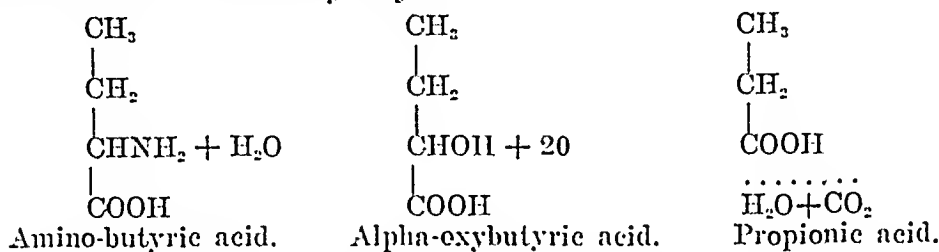
68. Joslin: *Jour. Med. Research*, 1904, xii, 433.

69. Embden, Salomon and Schmidt: *Beitr. z. chem. Physiol. u. Path.*, 1906, vi, 121.

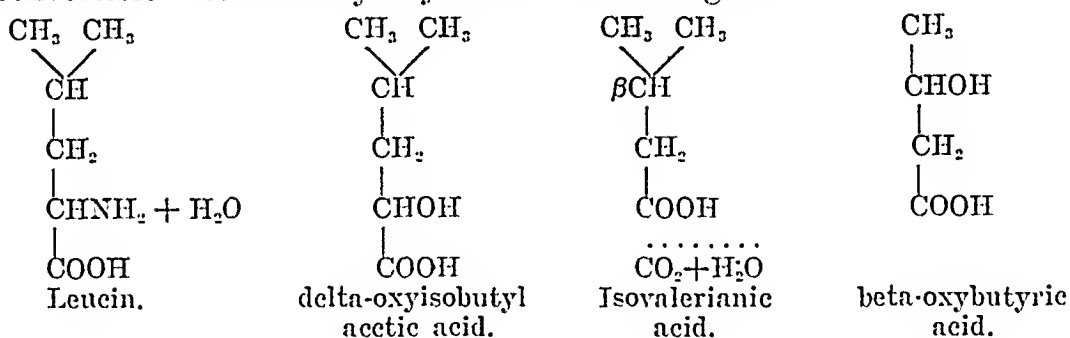
70. Baer and Blum: *Arch. f. exper. Path. u. Pharmacol.*, 1906, iv, 89.



In a similar manner amino-butyric acid and amino-caproic acid would produce, respectively, propionic and valerianic acids, neither of which are convertible into beta-oxybutyric.



In the case of leucin, iso-valerianic acid would be the intermediary product, and it has been shown that this fatty acid with its broken chain is convertible into beta-oxybutyric acid in the organism.



Amino-acids which form sugar on ingestion, such as glycocoll, alanin, aspartic acid and glutamic acid, do not form beta-oxybutyric acid, but may rather decrease the quantity produced, especially if the sugar formed can burn. This explains why the acidosis in fasting is reduced on ingestion of meat. Baer and Blum<sup>71</sup> gave 10 gm. of alanin to a dog which received about a gram of phlorhizin daily. The sugar output was raised from 19.5 to 21.5 gm. Since we have seen that alanin is completely convertible into dextrose, it follows that much of it must have been burned in the incompletely phlorhizinized dog. Therefore, the acetone excretion decreased and beta-oxybutyric acid disappeared. The profound effect of the ingestion of glutaric acid in reducing sugar and nitrogen output as well as the acetone bodies may find a similar explanation. It is absolutely certain that the skilfully planned work of Baer

71. Baer and Blum: Beitr. z. chem. Physiol. u. Path., 1907, x, 90.

and Blum loses a large part of its significance because of the two small and too frequent dosage with phlorhizin.

Magnus-Levy<sup>72</sup> gave 11.7 gm. of beta-oxybutyric acid to a normal dog. This was completely burned. He then gave 11.5 gm. to a phlorhizinized dog, with the result that there was an increased elimination of 7.6 gm. of beta-oxybutyric acid and acetone. Since some acetone was eliminated in the breath, it is evident that the animal had largely lost the power to burn ingested beta-oxybutyric acid.

Whatever will materially reduce the metabolism of fat in the body will evidently diminish the source of beta-oxybutyric acid. Such a substance is alcohol. Thus, Benedikt and Török<sup>73</sup> were able to reduce the acetone excretion, as well as that of nitrogen and dextrose after administering alcohol to a diabetic. Stäubli,<sup>74</sup> however, states that alcohol may reduce the tolerance of the diabetic for carbohydrate. Unfortunately, the administration of galactose, levulose and of pentoses are of little value in diabetes. In severe cases levulose is largely converted into dextrose or eliminated in the urine. Stäubli finds that ingestion of levulose reduces the diabetic's tolerance for dextrose. Brasch<sup>75</sup> finds that the pentoses rhamnose, arabinose and xylose are not convertible into dextrose in the organism of phlorhizinized dogs; they tend to raise the protein metabolism. Similar results have been obtained in man, and in man pentoses also produce diarrhea.<sup>76</sup>

On the basis of work on a diabetic and comatose boy weighing 32 kg., Magnus-Levy<sup>77</sup> makes the following computation of metabolism. He purposely assumes a high requirement of energy for a lad of this size, or 50 to 55 calories per kilogram, which calls for a total of 1,600 to 1,700 calories. The boy burned 90 gm. of protein and perhaps 200 gm. of fat:

$$\begin{array}{rcl}
 90 \text{ gm. protein} & = & 369 \text{ calories} \\
 200 \text{ gm. fat} & = & 1,909 \text{ calories} \\
 \left. \begin{array}{l} 90 \text{ gm. protein} = 369 \text{ calories} \\ 200 \text{ gm. fat} = 1,909 \text{ calories} \end{array} \right\} & \dots\dots\dots & = 2,278 \\
 \text{Deduct } 97.5 \text{ gm. oxybutyric acid, } & 443 \text{ calories} & \\
 \text{Deduct } 50 \text{ gm. urinary sugar, } & 185 \text{ calories} & \\
 \left. \begin{array}{l} \text{Deduct } 97.5 \text{ gm. oxybutyric acid, } 443 \text{ calories} \\ \text{Deduct } 50 \text{ gm. urinary sugar, } 185 \text{ calories} \end{array} \right\} & = & 628 \\
 \hline
 \text{Calories available} & \dots\dots\dots & 1,650
 \end{array}$$

Here we perceive an extreme case of diabetic metabolism in which half the energy contained in protein is excreted in urinary sugar and 20

72. Magnus-Levy: *Ergebn. d. inn. Med.*, 1908, i, 372.

73. Benedikt and Török: *Ztschr. f. klin. Med.*, 1906, lx, 329.

74. Stäubli: *Deutsch. Arch. f. klin. Med.*, 1908, cxiii, 125.

75. Brasch: *Ztschr. f. Biol.*, 1907, l, 115.

76. Von Jaksch: *Deutsch. Arch. f. klin. Med.*, 1899, lxiii, 612.

77. Magnus-Levy: *Ergebn. d. inn. Med.*, 1908, i, 385.

per cent. of that contained in fat is eliminated in the unburned beta-oxybutyric acid.

This, then, is the worst picture of the perverted metabolism in diabetes. Sugar can not burn, fat burns only as far as beta-oxybutyric acid, and as for protein a part of its amino-acids are converted into sugar and another part into beta-oxybutyric acid, neither of which can be burned.

Rosenfeld has said that fat can burn only "in the fire of carbohydrates." But this is not true. Mandel and I, in our work on a diabetic with a D:N ratio of 3.65 to 1, and who had no tolerance for carbohydrates, found a low acidosis as measured by a maximum excretion of 2 gm. of ammonia, no beta-oxybutyric acid, and a maximum of 0.8 gm. of acetone per day. On the other hand, von Noorden<sup>78</sup> and Magnus-Levy<sup>79</sup> report cases in which there was a considerable excretion of acetone bodies in the urine when carbohydrates were burned. For example, one patient eliminated 4.9 gm. of beta-oxybutyric acid on a day when 40 gm. of starch were ingested and burned. There are great individual variations. Thus, Stäubli<sup>80</sup> reports concerning a diabetic man whose ordinary mixed diet was changed to one of meat and fat, including 50 gm. of bread, the whole containing 3,200 calories. After ten days of this diet, during which the sugar output remained nearly constant at 100 gm., the beta-oxybutyric acid fell from 37.5 gm. daily to nothing. In commenting on his results Stäubli says: "The important factor which causes a more serious condition in the metabolism of a diabetic is the quantity in which carbohydrate is administered in excess of the tolerance for sugar. Damage caused by a continual overworking of the sugar-burning capacity plays a large part in the progress of the disease. The considerable withdrawal of carbohydrates from the diet, even in cases of severe diabetes with high acidosis, exerts an extraordinarily beneficial influence. This can be, in part, explained by the increased ability to burn sugar on account of the conservation of the body's power in this direction. The improvement in the capacity for sugar combustion exerts on its side a beneficial action on the acidosis."

The damage done in severe diabetes by flooding the organism with carbohydrates is illustrated by a diabetic individual who had been kept on a restricted diet at my advice, but on the recommendation of a consultant was given a large quantity of carbohydrate; this resulted in onset of coma, which proved fatal.

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78. Von Noorden: *Pathologie des Stoffwechsels*, 1907, ii, 77.

79. Magnus-Levy: *Ergebn. d. inn. Med.*, 1908, i, 404.

80. Stäubli: *Deutsch. Arch. f. klin. Med.*, 1908, cxiii, 125.

The great individual variations as regards the presence of the acetone bodies seem to warrant the opinion which I expressed in a discussion on acidosis at Washington two years ago, that one may assume the existence of a specific beta-oxybutyric acid ferment analogous to the ferment which breaks down the sugar. Such a ferment would split beta-oxybutyric acid, thereby performing the last offices of cleavage of the fatty molecules. Injury to this ferment may be complete or partial even as in the case of the sugar ferment, but damage to one does not necessarily involve proportionate damage to the other.

The elimination of beta-oxybutyric acid from the system is furthered by the administration of alkalis. Stäubli<sup>80</sup> reports a diabetic who eliminated 34 gm. of beta-oxybutyric acid daily when the diet contained 60 gm. of sodium bicarbonate. This excretion fell to 17 gm. on a diet which was free from alkali, and then rose to 45.2 gm. on return to 60 gm. of bicarbonate. Such treatment with alkali is highly beneficial, for, as Magnus-Levy observes, the diabetic does not die in coma because of the neutralized acid which is eliminated in the urine, but rather on account of that which is retained in the body which neutralizes the alkalis of tissue and of body fluids.

Bedard, Pembry and Spriggs<sup>81</sup> find that the blood of the diabetic in coma still has considerable power to hold carbon dioxide in spite of the acidosis. They explain that the reduction of carbon dioxide in the blood is due to the extra ventilation brought on by dyspnea, and that the dyspnea is the result of acids rendering the respiratory center especially sensitive to carbon dioxide and other stimulating substances.

I have purposely traced the doctrine of diabetic metabolism through its most acute manifestations. There are, however, countless variations from the extreme conditions. The hope for the diabetic lies in dieting. His carbohydrate tolerance must be determined. Mandel and I<sup>23</sup> have recommended that the patient be put on a strict carbohydrate-free diet and the D:N ratio of the second day of the diet be determined. If the ratio be 3.65 to 1 it is the "fatal ratio" and represents a complete intolerance for carbohydrates. A lower ratio represents hope for the patient. Following this method we found the "fatal ratio" in one patient who died a month later. In another case of a young man revived from coma and placed on a meat and fat diet the D:N ratio fell steadily from 2.8 to 1 on the second day until the tenth day, when it was 0.34 to 1, and after three weeks the urine was free from sugar even after the ingestion of small quantities of carbohydrates. Two years later the ratio was 2.8

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81. Bedard, Pembry and Spriggs: *Jour. Physiol.*, 1904, xxxi, 46.

to 1 after a week of strict meat and fat diet, which indicated a less favorable outlook, although the patient maintained his weight and went about his usual occupation. A year later he died in coma.

A splendid piece of metabolism work on a diabetic man was published a year ago by Allard<sup>82</sup> from Minkowski's clinic at Greifswald. I have taken the liberty to rearrange the figures. The experiment was accomplished on a man weighing between 51 and 52 kg., who entered the hospital in a state of extreme emaciation. During residence in the hospital his weight improved. He was given various diets and allowed to fast, and account was kept of the nitrogen, dextrose, ammonia, beta-oxybutyric acid and acetone eliminated in the urine. The results may thus be tabulated:

EXPERIMENT BY ALLARD  
FROM MINKOWSKI'S CLINIC AT GREIFSWALD

Date.	Diet.	Period. hrs.	Urine. c.c.	N gm.	D gm.	D:N	NH <sub>3</sub>	Beta-oxy- butyric acid.	Ac- tone.	Total acids.
Feb. 22—	Meat fat	24	5130	32.9	105.6	3.25	5.2	17.34	5.88	23.22
Feb. 23—	Fasting	24	5395	14.0	30.6	2.11	3.1	2.95	1.82	4.77
Feb. 24—	300 gm. nutrose..	24	3070	27.6	95.5	3.47	4.0	2.86	1.68	4.55
Mar. 20—	Meat fat	24	4730	19.2	71.8	3.75	5.0	15.14	6.73	21.87
Mar. 21—	Fasting	12	2815	6.5	23.0	3.67	1.7	2.34	1.47	3.81
Mar. 21—	200 gm. butter..	12	2335	4.6	25.2	5.48	1.8	5.66	1.79	7.45
Apr. 6—	Meat fat	12	2195	15.7	52.0	3.34	2.6	8.43	4.05	12.48
Apr. 7—	Fasting	24	5155	13.6	16.4	1.21	3.4	6.28	2.98	9.26
Apr. 11—	200 gm. butter..	24	4905	13.0	40.1	3.08	4.0	16.03	5.67	21.71

This experiment shows the beneficial action of a fasting day on the acidosis of a diabetic. Thus, on February 22, when the patient ingested meat and fat, the total acetone bodies amounted to 23 gm. in twenty-four hours, and on February 23, during fasting, they fell to 4.8 gm. The ammonia was also greatly reduced. The D:N ratio fell from 3.25 to 2.11. On February 24, 300 gm. of nutrose (a sodium compound of casein) were given, without raising the acidosis above the fasting amount, but the D:N ratio became 3.47. On March 20, on a meat-fat diet, the acidosis was again high and the D:N ratio was 3.75. The next day of fasting the acetone bodies fell very largely and the D:N ratio remained at 3.67. These represent the maximum ratios in diabetes as I understand them. On March 21, 200 gm. of butter were given, causing a rise in the acidosis and a rise in the ratio to 5.48. Whether this high ratio is due to nitrogen retention or to the conversion of glycerin into dextrose can not be determined. In the light of other evidence it is not probable that any of the fatty acids ingested were converted into dextrose. A fasting day on April 7 showed a low acidosis and a D:N

82. Allard: Arch. f. exper. Path. u. Pharmacol., 1907, lvii, 1.



ratio of 1.21. An improvement in the power to burn dextrose had, therefore, taken place, although it appears remarkable that this was not accompanied by a decreased elimination of nitrogen and acetone bodies, as contrasted with the amounts excreted on former fasting days when the D:N ratio was higher. On April 11 the improvement in the ratio was largely nullified by the ingestion of 200 gm. of butter. The excretion of acetone bodies rose from 9 to 22 gm. and the D:N ratio rose to 3.08. Apparently a high acidosis lowers the tolerance for carbohydrate, just as large ingestion of carbohydrates lowers the tolerance for beta-oxybutyric acid. This experiment does not justify the assumption of Mandel and myself, that the "fatal ratio" once established will continue throughout life. I have presented this table to indicate to you a high type of modern clinical work.

There is no cure for diabetes. Only dieting relieves the sufferer. Of the results of dieting, Dr. Falta, speaking with the authority of von Noorden's great clinic, and of his own good work, will address us at the next Harvey Society Lecture.

Extracts of the pancreas and the ferments of yeast are without effect. Falta<sup>83</sup> has subcutaneously injected a normal dog's serum into a dog with pancreas diabetes without changing the D:N ratio, and again he has introduced the lymph of a normal dog, drop by drop, into the femoral vein of a diabetic dog without result.

Physicians call on the laboratories for a cure, but there is no cure. All that the laboratories can furnish are indices whereby relief may be rendered. It is easy enough to give the results of the gross activities of many million millions of cells in terms of so many grams of sugar or of nitrogen or of beta-oxybutyric acid, but it is not easy to gain access to a mystery which is at present the hidden secret of microscopic particles. But we must not despair. The great physiologist, Johannes Müller, stated that no man would ever measure the rapidity of the nerve impulse, and ten years later his pupil, Helmholtz, measured it. It is to the increasing number of young men who are attracted by the scientific or intellectual side of medicine that the world hopefully turns for relief from the miseries of its diseases.

University and Bellevue Hospital Medical College.

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83. Falta: *Wien. klin. Wchnschr.*, 1907, No. 49.

# THE ANATOMIC EXPLANATION OF THE GREATER AMOUNT OF VOCAL FREMITUS AND VOCAL RESONANCE NORMALLY FOUND AT THE APEX OF THE RIGHT LUNG \*

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PHILADELPHIA

## HISTORICAL

Writers on physical diagnosis have for many years agreed that in the normal chest both vocal fremitus and vocal resonance are more marked on the right side than on the left. This phenomenon, according to Walshe,<sup>1</sup> was first noted by Stokes, but the original statement I have been unable to find in the available published writings of Stokes.

Skoda,<sup>2</sup> in his classical work on auscultation and percussion, Markham's translation of which was published in 1854, states that "the voice of the same individual, whether his thoracic organs be healthy or unhealthy, is not heard equally loud at all parts of the thorax," but the concrete fact of the normal difference between the two sides evidently escaped him, as he makes no mention of it.

Walshe,<sup>3</sup> in 1860, states of fremitus: "As a general rule, the intensity of the fremitus is considerably greater on the right side of the chest than on the left, the greatest amount of this excess existing in the infraclavicular, infrascapular and interscapular regions." "The fremitus is intensely marked over the larynx and trachea, stronger at the sternal than the humeral halves of the infraclavicular regions, generally faintly manifest on the right clavicle, and imperceptible at the top of the sternum." "In the great majority of cases it is stronger in recumbency than in the sitting position."

Concerning vocal resonance the same writer<sup>4</sup> says: "The intensity and quality of this natural resonance are modified by certain circum-

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\*From the Laboratory of Anatomy of the University of Pennsylvania. Read at a staff meeting of the Henry Phipps Institute, Dec. 21, 1908.

1. Walshe (Walter Hayle): A practical treatise on diseases of the lungs, including the principles of physical diagnosis, ed. 3, 1860, p. 142.

2. Skoda (Joseph): Auscultation and percussion. Transl. from 4th German ed. by W. O. Markham, 1854, p. 65.

3. Walshe (Walter Hayle): A practical treatise on diseases of the lungs, 1860, p. 28.

4. Walshe (Walter Hayle): A practical treatise on diseases of the lungs, 1860, pp. 141-142.

stances altogether independent of disease. Thus the natural resonance is, *cæteris paribus*, marked in proportion to the graveness of the voice. This statement is only true of intensity, however; there is no greater tendency to concentration or articulation of the sound when the voice is grave than when it is shrill. Secondly, vocal resonance is, as a corollary from the last proposition, more marked in males and adults than in females and children; it is also more marked in aged persons than in adults, doubtless on account of the wasting of the pulmonary parenchyma and the thickening and hardening of the bronchi in old age. Thirdly, the quality of the resonance varies with the quality of the speaking voice; thus in people of advanced years it is very commonly tremulous and bleating. Fourthly, the resonance is more strongly developed the larger the chest and the less loaded its walls with fat and muscle. Fifthly, it is stronger in front than behind, with the exception of the inter-seapular region, and at the upper than the lower parts of the thorax. Sixthly, as first stated by Dr. Stokes, its intensity is greater on the right side generally than the left—a fact chiefly significant, though by no means valueless elsewhere, under the clavicles and in the interseapular region; there is no resonance over the superficial cardiac region, nor over the hepatic surface below the sixth rib. Seventhly, the intensity of vocal resonance, as of the respiratory sounds, varies much in persons apparently presenting the same physical conditions for its development.”

Landois and Stirling,<sup>5</sup> in 1885, state that “bronchial breathing is slightly louder on the right side.”

Hare,<sup>6</sup> in 1897, says: “Vocal fremitus is also greater on the right side than on the left.”

Musser,<sup>7</sup> in 1899, says of vocal fremitus: “The fremitus on the right side at the apex is stronger than on the left.” Of vocal resonance he states: “It is heard more pronouncedly at the right apex than at the left.”

Sabli,<sup>8</sup> in 1905, says concerning vocal fremitus: “The fremitus is normally somewhat stronger on the right than on the left side.” As regards physiologic bronchial breathing he states: “This breathing is naturally more evident on the right side.”

It is needless further to multiply quotations on this point, as, beginning about the middle of the last century, a gradually increasing number

5. Landois and Stirling: A text-book of human physiology. Transl. from 4th German ed., 1885, i, 245.

6. Hare (Hobart A.): Practical diagnosis, ed. 2, 1897, p. 273.

7. Musser (John H.): Medical diagnosis, ed. 3, 1899, pp. 490 and 513.

8. Sabli (Hermann): Diagnostic methods. Transl. from 4th German ed., 1905, pp. 222 and 288.

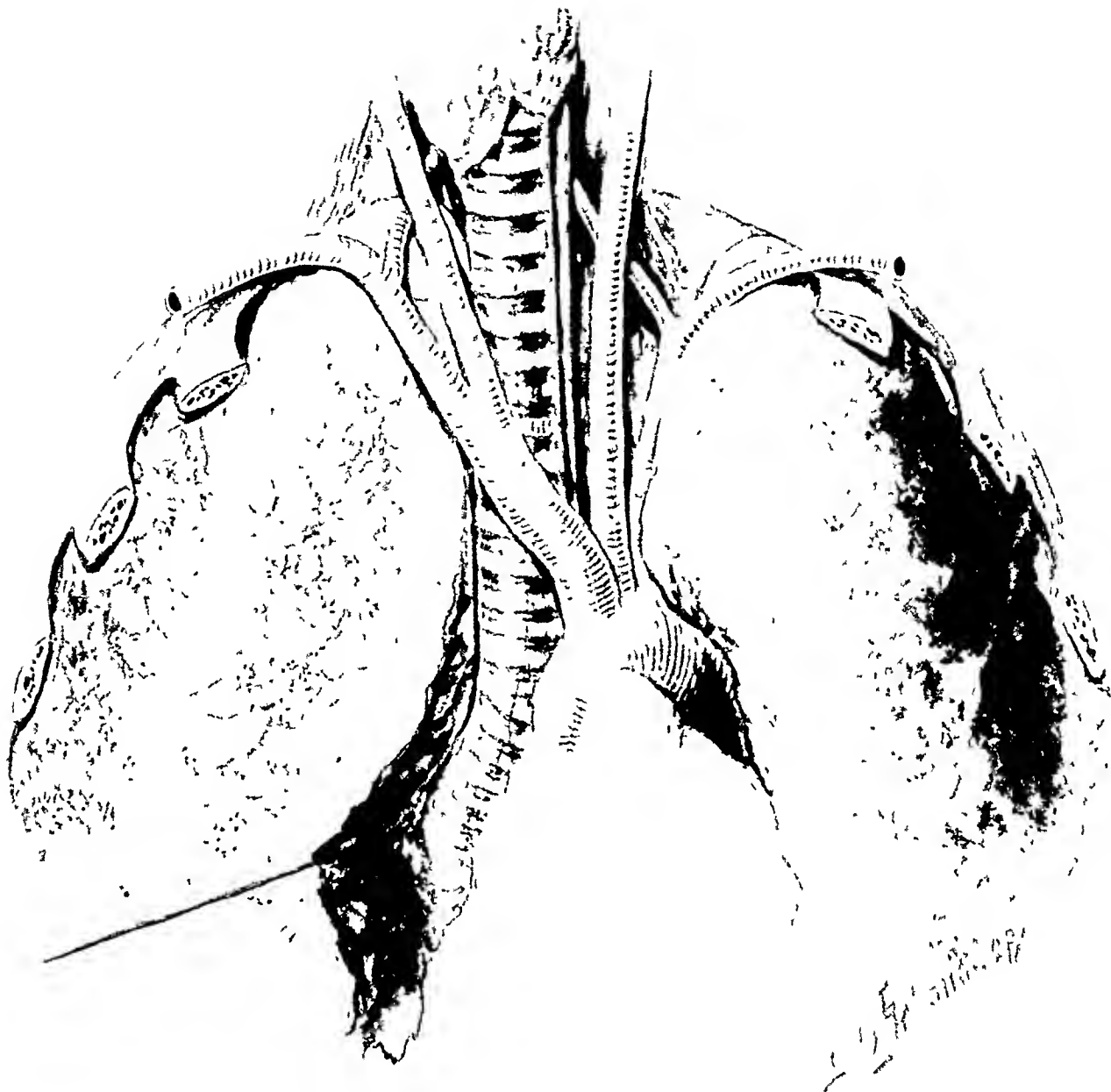


Fig. 1.—Drawing of a dissection of the upper part of the thorax. For the sake of simplicity, the veins and the smaller branches of the subclavian artery have been omitted. This figure shows in plastic form those relations in the upper thorax which are demonstrated in photographs in succeeding figures. There is here shown clearly the interposition of the left subclavian and common carotid arteries between the trachea and the left upper lobe, as well as the apposition of the trachea and the right upper lobe, with the large vessels anterior.



of authorities on diagnosis state the truth of the observation, and at the present time it is a matter of common acceptance.

To explain the condition several theories have been advanced. Walshe offers no explanation, satisfying himself with a mere statement of the fact.

Landois and Stirling<sup>5</sup> state that the reason is the "slightly greater caliber of the right bronchus."

Hare<sup>6</sup> ascribes as the reason for the difference the fact that "the principal bronchus supplying this lung is larger than that of the left side, is joined to the trachea at a less acute angle, and is nearer the vertebral column; and, again, as recently emphasized by Cary, the bronchus going to the right upper lobe is given off at a point very near the origin of the right bronchus, and in many cases 'fully two and a half inches above the corresponding left bronchial tube.'"

Musser<sup>7</sup> quotes Ewart and Cary in support of the theory that the condition is due to the fact that "the right bronchus is larger than the left, its angle with the trachea is more acute, and the bronchus going to the right upper lobe is two and a half inches nearer the larynx than the left."

Sahli<sup>8</sup> says that the phenomenon is due to "the greater breadth and the more direct branching of the right bronchus."

#### ANATOMIC CONSIDERATIONS

As the discrepancy between the two sides is evidently due to differing anatomic conditions it may not be amiss to review the relations of the trachea, bronchi and lungs in the upper part of the thorax. In so doing several suggestive points can be brought out.

*The Course of the Trachea.*—This tube extends from the inferior margin of the cricoid cartilage through the lower part of the neck and the upper part of the thorax to a point opposite the lower margin of the manubrium sterni in front and the lower edge of the fourth thoracic vertebra behind. At this situation it divides into the two bronchi. In its course down the neck and thorax, especially the latter, it inclines to the right, probably on account of the position of the arch of the aorta to its left side. Its point of bifurcation usually lies to the right of the midsternal line, sometimes so far over as to be behind the right margin of the sternum (Fig. 2).

*The Relations of the Trachea.*—In the thorax these are as follows: Posterior to it, at its origin, lies the esophagus, which at first is directly behind, but later moves to the left to such an extent that in the upper part of the posterior mediastinum it lies behind the left bronchus (Fig.

4). The recurrent laryngeal nerves also lie behind the trachea. In front are the first part of the arch of the aorta and just above the latter, the origins of the innominate and left common carotid arteries (Fig. 1), in front of which are the left innominate vein and the remains of the thymus body. The innominate artery, as it passes upward, lies anterior to the upper lobe of the right lung, while the left common carotid seeks a deeper plane and ascends at the left side of the trachea (Fig. 3). Just above and anterior to the tracheal bifurcation is the deep cardiac plexus of nerves. On the left side, above the left bronchus, is the backward coursing arch of the aorta (Fig. 4), which makes an indentation, sometimes quite marked, in this wall of the trachea. Further up are the left vagus nerve and the left common carotid artery (Figs. 1 and 3), and these, with the aorta, the left subclavian artery, the esophagus and a quantity of areolar and lymphatic tissue (Fig. 3), form a layer several centimeters thick which separates the left lung from the trachea. On the right side the trachea has touching it the right vagus nerve (Fig. 6) and the mediastinal part of the right parietal pleura (Figs. 3 and 4), the latter lying in contact with the trachea from the base of the neck to the origin of the right bronchus (Fig. 4).

*The Bifurcation of the Trachea.*—This, as stated above, occurs at a point opposite the lower end of the manubrium sterni anteriorly or the lower edge of the fourth thoracic vertebra posteriorly, and usually to the right of the median line (Fig. 2). The carina tracheæ (Fig. 4) is a keel-like lunate ridge which separates the origin of the two bronchi and in the majority of instances lies to the left of the tracheal midline. Heller and von Schrötter, in 100 cadavers, found it on the left side in 57 per cent. and in the middle in 42 per cent (Dwight<sup>9</sup>). Sir Felix Semon found it, in the living, on the left in 59 per cent., in the middle in 35 per cent. and on the right in 6 per cent (Dwight<sup>9</sup>). Lying under the angle of bifurcation and connecting the bronchi is the interbronchial ligament, under which is a group of lymph nodes.

*The Caliber of the Bronchi.*—The right bronchus is wider than the left in the proportion of 100-77.9, the extreme being 100-71.6 and 100-83.3, and in 10 per cent. the caliber being about equal (Braune and Stahel, quoted by Dwight<sup>9</sup>). As a practical working basis this proportion can be considered as being 100-75.

*The Angle of Origin of the Bronchi.*—The right bronchus is the more vertical of the two, forming an angle of 24.8 degrees with the body axis, while the left comes off at an angle of 45.6 degrees (Cunning-

9. Dwight (Thomas): Piersol's human anatomy, 1907, pp. 1837-1838.

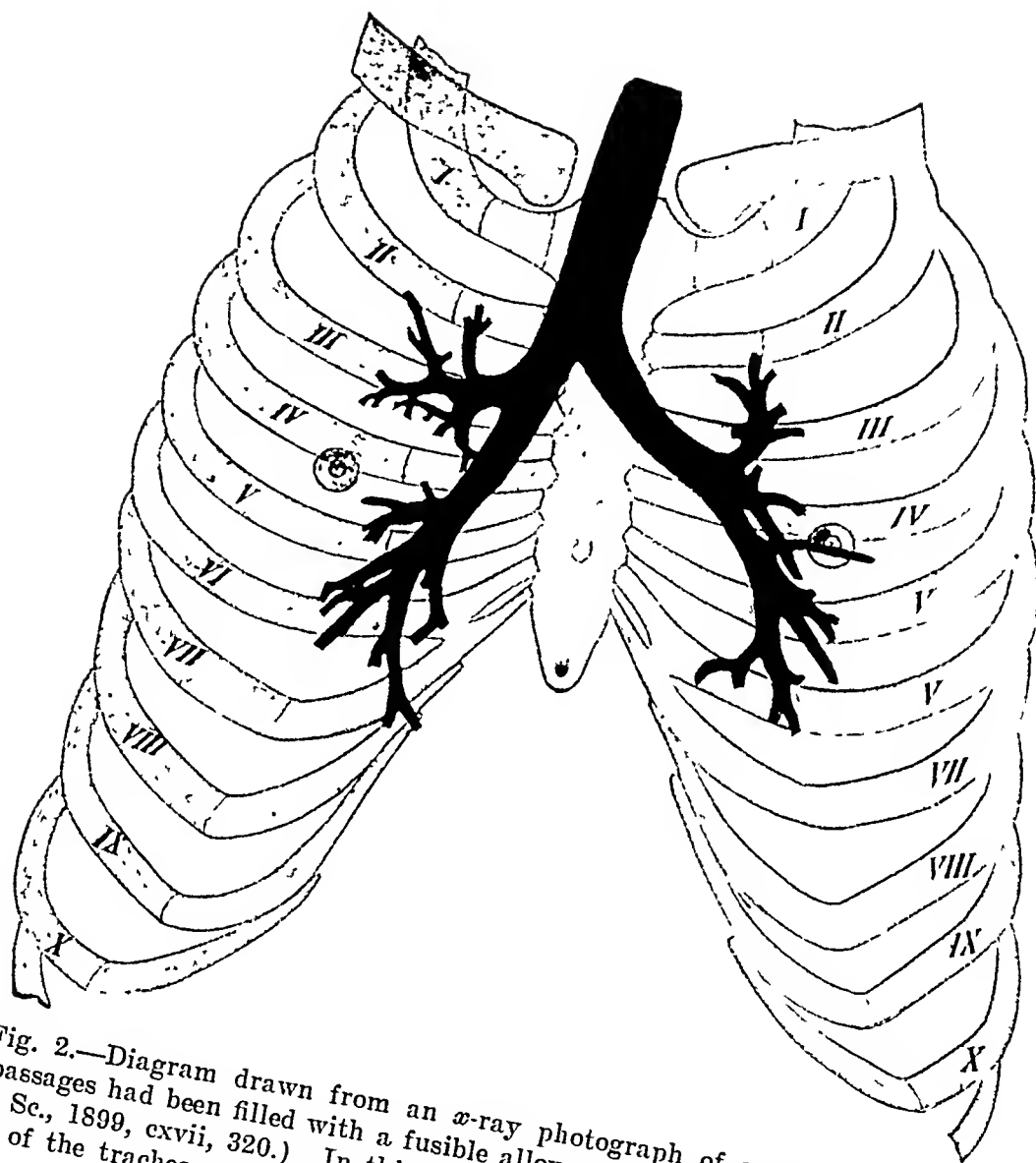


Fig. 2.—Diagram drawn from an *x*-ray photograph of a chest in which the air passages had been filled with a fusible alloy. (Blake [Joseph A.]: *Am. Jour. Med. Sc.*, 1899, cxvii, 320.) In this diagram will be noted the inclination to the right of the trachea, and the right lateral position of the bifurcation.





ham<sup>10</sup>), or, in simpler figures, 25 degrees and 45 degrees, the subtracheal angle, therefore, being about 70 degrees.

*The Length of the Bronchi.*—According to Ewart,<sup>11</sup> the following measurements have been ascertained for the bronchi from their origin to their first branch:

Right bronchus 21.1 mm., left bronchus 49 mm. (Aeby).

Right bronchus 15-18 mm., left bronchus 30-35 mm. (Sappey).

Right bronchus 25 mm., left bronchus 50 mm. (Quain).

I have made these measurements in one body (Fig. 6), in which a section of the thorax had been made in the long axis of the trachea after injecting with formalin and freezing. A possible source of error in the results was the presence in the specimen of bilateral pulmonary tuberculosis. This body gave a length of 35 mm. on the right side and 45 mm. on the left. Measurements taken in a specimen so prepared are the only ones of real value, for if the measuring be done after removal of the organs from the body there is so much unavoidable displacement and stretching that the normal relations are seriously disturbed. In addition, after removal, the natural greater length of the left tube would be exaggerated on account of relatively and actually greater stretching.

*The Branches of the Main Bronchi.*—The left bronchus passes in an unbranched condition into the lung and there bifurcates into two branches, one for the upper lobe and one for the lower lobe, although their distribution does not actually correspond to this description. The right gives off the upper lobe bronchus, called the eparterial bronchus on account of its position relative to the pulmonary artery, and then continues as the bronchus intermedius to the lung, where it divides into the middle lobe bronchus and the lower lobe bronchus.

*The Right Upper Lobe Bronchus or Eparterial Bronchus (Aeby).*—This tube lies in the horizontal plane and is distributed solely to the upper lobe. It measures 15 mm. in length (Ewart<sup>12</sup>), the measurements being taken on the outer surface of a cast of the tube made after removal of the respiratory organs from the body. In the one specimen measured I found the length of this tube to be 20 mm. At its termination it divides into a pectoral stem and an axillary-apical stem, the latter measuring 3 mm. After continuing on for 8 mm. the latter divides into an ascending apical and an axillary stem. It will thus be seen that, accepting Ewart's measurements, the distance from the bifurcation of the

10. Cunningham (D. J.): The text-book of anatomy, ed. 2, 1906, p. 976.

11. Ewart (William): The bronchi and pulmonary blood-vessels, 1889, p. 71.

12. Ewart (William): The bronchi and pulmonary blood vessels, 1889, p. 90.

trachea to the origin of the right apical bronchus is 39.1 mm. ( $21.1 + 15 + 3$ ).

*The Left Upper Lobe Bronchus or Bronchus Impar (Ewart).*—The left/main bronchus enters the lung without having branched, and after gaining the pulmonary parenchyma it divides into the upper lobe bronchus and the lower lobe bronchus.

The former differs from the corresponding structure on the right side in that it is hyparterial in position, it supplies not only the upper lobe but also the cardiac district of the lower, and its two branches correspond, respectively, to the eparterial and middle lobe bronchi of the right side. It measures 13 mm. (Ewart<sup>13</sup>) and in diameter equals that of the right side. It terminates by dividing into an ascending and a descending branch. The former measures 8 mm. in length and ascends to give off a pectoral branch and to continue on as an axillary-apical branch, which breaks up into three, all of which engage in the supply of the apex. The distance, therefore, from the bifurcation of the trachea, according to Ewart's figures, is 70 mm. ( $49 + 13 + 8$ ), the measurements being carried no further on this side on account of the entire axillary-apical trunk supplying the pulmonary apex.

There is thus an apparent difference between the two sides of 30.9 mm., the greater length being, of course, on the left side.

In the one specimen I measured the distance from the origin of the eparterial bronchus to the axillary-apical bronchus was 20 mm. and from the origin of the left upper lobe bronchus to that of the axillary-apical bronchus was 12 mm.; the resultant figures show that, on the right side, the distance from the tracheal bifurcation to the axillary-apical bronchus was 55 mm. and on the left 57 mm., a difference of only 2 mm. This is undoubtedly less than the average, due possibly in part to the pulmonary disease and in part to an unusually lateral origin of the eparterial bronchus, but it suggests strongly that some of the accepted figures may be somewhat untrustworthy.

#### ACCEPTED EXPLANATIONS

Sufficient data are now at hand to enable us to examine into and perhaps readjust and add to the accepted theories. There are three of these, one being the more direct continuation of the right bronchus into the line of the trachea, another the shorter distance from the bifurcation of the trachea to the right apex, and the third the greater caliber of the right bronchus.

13. Ewart (William): The bronchi and pulmonary blood vessels, 1889, p. 98.



Fig. 3.—Section through the upper part of the thorax, viewed from below. The line of section is not exactly horizontal, a slightly lower plane being reached on the right side than on the left. In order to show the apical part of the right pleura, the pulmonary apices have been removed. There can be noted in this specimen the beginning of the right pleura with the trachea, and the anterior position of the innominate artery, whose bifurcation is well shown. On the left side, the wide separation of the pleura from the trachea by means of the large arteries, the esophagus and areolar tissue can readily be seen. T, trachea; E, esophagus; RAP, right apical pleura; LAP, left apical pleura; IA, innominate artery, dividing into RSA, right subclavian artery and RCA, right common carotid artery; LSA, left subclavian artery; LCA, left common carotid artery; RSV, right subclavian vein; LIV, left innominate vein.





Fig. 4.—Vertical section, viewed from in front, of the thorax on a plane just posterior to the origin from the aorta of the left common carotid artery. After the section had been made, the loose areolar tissue was dissected out to demonstrate more clearly the vessels, etc. There is shown plainly the contact of the right upper lobe with the trachea. T, trachea; CT, carina tracheae; E, esophagus; RVN, right upper lobe; LUL, left upper lobe; A, aorta; LCA, left common carotid artery; LSA, left subclavian artery; RSA, right common carotid artery; RCA, right common carotid artery; LPA, left pulmonary artery; LPV, left inferior pulmonary vein; LMA, left internal mammary artery.



1. The more vertical course of the main bronchus of the right side and its consequent more direct continuity with the trachea.—Assuming for the present that the vocal vibrations are transmitted to the surface of the apex solely by way of the air content of the bronchi and lungs, it is hard to see how the angle of the right main bronchus can be of any ultimate effect. If we apply to this tube the rule that the volume of sound transmitted, it must apply equally well to all subsequent branchings. Reduced to the last analysis, vocal sound waves transmitted by the air current to the apex must pass through an angle of 180 degrees; they must pass down, they must pass laterally; they must pass up, this truth applying with equal force to both sides. Now, if the right bronchus subtract but 25 degrees from the 180 degrees, it leaves 155 degrees still to be traversed before the waves pass upward, and what is gained at the first point is lost by later branchings. On the other hand, with the left system of tubes 45 of the 180 degrees are subtracted at once, and it is quite possible that the vibrations may be less marked in the left bronchus than in the right. At the same time the preponderance should cease at this point, as there is remaining on the left side only 135 degrees, as opposed to 155 degrees on the right, to be traveled in order to reach the apex. In other words, what is lost at the bifurcation of the trachea is gained further on at the subsequent branchings of the bronchial system. Does it not follow, therefore, that the direction of the right bronchus, eliminating all other considerations, can have no effect in causing greater fremitus and resonance on the right side?

2. Distance.—It is stated quite truthfully that the vocal sounds, to reach the left apex, must travel a greater distance than to reach the right. According to Ewart's figures, in order to reach the origin of the axillary-apical bronchus, vocal vibrations have 30.9 mm. farther to travel on the left side than on the right. While this may be the case, there are two possibilities to be considered in this connection. One is that the difference is not so great as our accepted figures would incline us to think. It will be recalled that in the one specimen in which I made measurements the difference between the two sides was but 2 mm. While this may be and probably is below the average, I am convinced from the study of a number of cadavers that the figures given by Ewart are too high. And Cary's<sup>14</sup> estimate of two and a half inches' difference between the origins of the upper lobe bronchi on the two sides certainly seems to be somewhat excessive. But even if it be correct there is

14. Cary (Charles): Tr. Assn. Am. Phys., 1895, p. 400.



not the ultimate difference that these figures would indicate, for the lower position of the summit of the left apex would subtract quite considerably from the given two and a half inches. It can be accepted, however, that the sound vibrations, to reach the axillary-apical bronchus, do have on the right side a shorter distance to travel than on the left. The second point to be considered is the position of the apices relative to each other and to the origin of the axillary-apical bronchus. As a rule that of the right is the higher, to the extent of 10-20 mm. (Figs. 4 and 6). One thorax (Fig. 6) especially prepared at the University showed a distance from the axillary-apical bronchus to the top of the apex of the lung on the right side of 70 mm. and on the left of 83 mm., a difference of 13 mm. This apparent contradiction is due to the fact that the left axillary-apical bronchus arises at a lower plane in the thorax than does the right. If, now, we allow 15 mm. as a fair average difference in length of path from tracheal bifurcation to axillary-apical bronchus and add to this 10 to 15 mm. difference between the origin of the axillary-apical bronchus and the apex, we have a greater distance of 25 to 30 mm. which the sound waves have to travel in the left lung. How much of an element in the problem this distance comprises is impossible to state, but when it is considered that in our stethoscopes a shortening or lengthening of the rubber tubes to the extent of many inches seems to have no effect on the clearness or intensity with which sounds are transmitted to the ear, it would seem that the importance attached to the 2 to 3 cm. difference is too great.

3. Caliber.—The right main bronchus is larger than the left in approximately the ratio of 100-75 (100-77.9, Braune and Stahl<sup>10</sup>). It has been customary to assign to this greater width all or some of the responsibility for the preponderance of fremitus and resonance on the right side. It is possible that this greater width may have some bearing on the question, but to decide this one must first inquire into the reason for the existence of the greater caliber. The answer is naturally that the right bronchus is wider than the left because it has more lung to supply. This being the case, would not the greater facility with which sound waves are transmitted through the right bronchus be later lost at the apex, on account of the greater peripheral area of pulmonary tissue to which these waves have to be distributed? It would seem, therefore, if this be accepted, that the greater caliber of the right bronchus may be responsible to some slight, but certainly not to any very marked degree.

#### AUTHOR'S EXPLANATION

Writers hitherto, in discussing the point at issue, have assumed that the vibrations responsible for the perception of fremitus and resonance

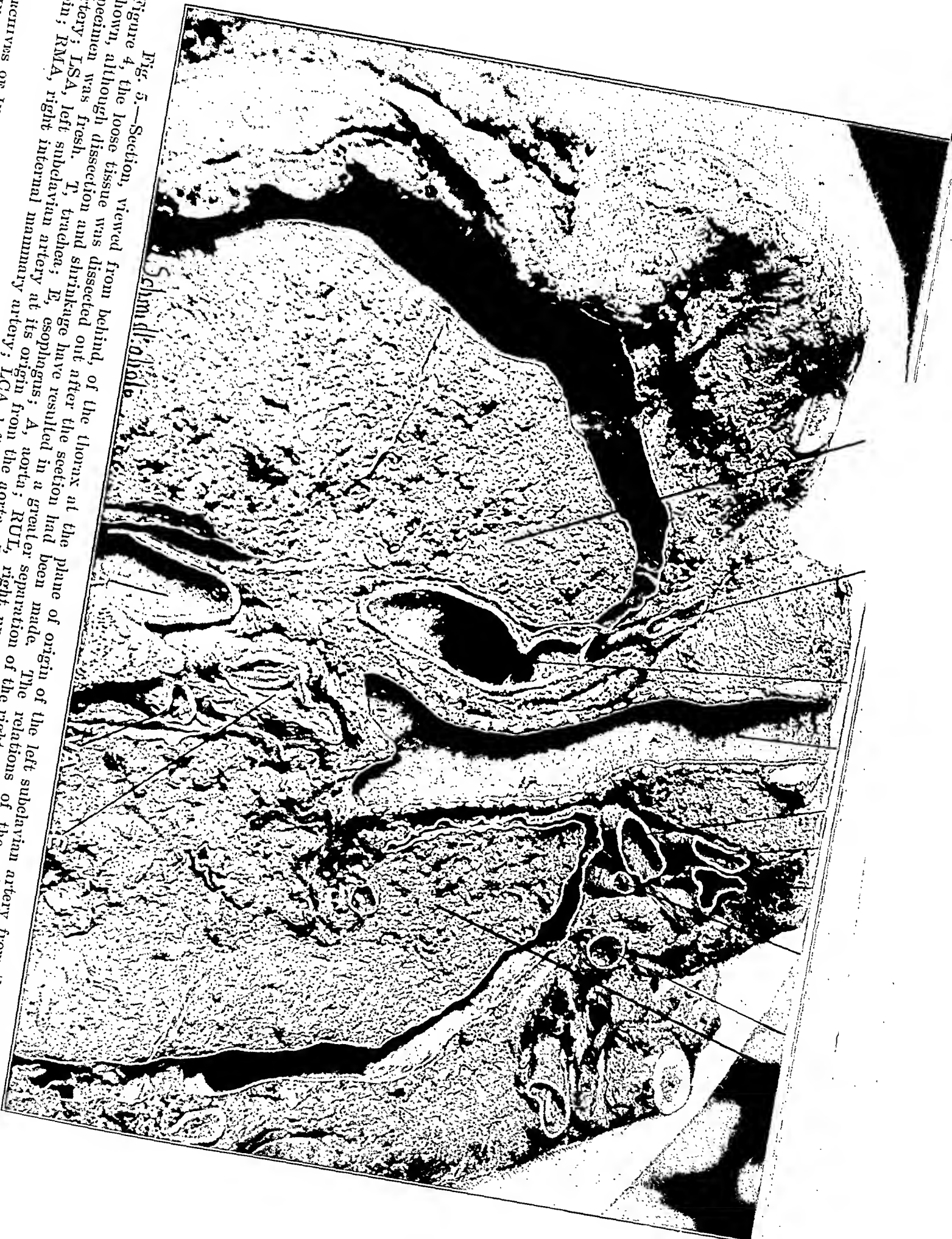


Fig. 5.—Section, viewed from behind, of the thorax at the plane of origin of the left subclavian artery from the aorta. As in shown, although dissection and shrinkage have resulted in a greater separation of the right upper lobe from the trachea apices are clearly artery; ISA, left subclavian artery; T, trachea; E, esophagus; A, aorta; RUL, right upper lobe, LUL, left upper lobe; RSA, right subclavian vein; RMA, right internal mammary artery; LCA, left common carotid artery; VA, vena azygos.

ARCHIVES OF INTERNAL MEDICINE  
 ILLUSTRATING ARTICLE BY DR. GEORGE PETERHOLZ





Fig. 6.—Section of the thorax, viewed from in front, cut in the axis of the trachea and main bronchi. The black pins show corresponding points on the two sides. The white pin on the right side marks the origin of the axillary-apical bronchus and on the left the division of the upper lobe bronchus into ascending and descending branches. In the plane in which the section is cut the right parietal pleura does not touch the trachea, because of tuberculous enlargement of the bronchial lymph nodes, some of which have been removed to show the vagus nerve. In a plane slightly posterior the pleura does touch the trachea. T, trachea; E, esophagus; A, aorta; RUL, right upper lobe; LUL, left upper lobe; RSA, right subclavian artery; RSV, right subclavian vein; RJV, right internal jugular vein; RVN, right vagus nerve; LCA, left common carotid artery; LSV, left subclavian vein; LPA, left pulmonary artery; BLN, enlarged bronchial lymph nodes; VA, vena azygos; AAB, origin of the right axillary-apical bronchus; ADU, division into ascending and descending branches of the left upper lobe bronchus.



at the apices have been transmitted from the larynx solely by the bronchial and pulmonary air. And this in spite of the fact that these sounds are elicited only during the outward passage of the air, during an expiratory puff, and, therefore, necessarily transmitted against the air current. But in the explanation afforded by the size, length and angle of the air tubes another possibility has been entirely lost sight of, and that is the direct transmission of vocal vibrations from the trachea through the tissues of the superior mediastinum to the lung apices. The trachea is about 10 cm. long, with approximately two-fifths of its length in the neck and three-fifths in the thorax. On its right side, almost entirely throughout its thoracic course, the lung lies in contact with it (Figs. 1, 3, 4 and 5), separated only by the parietal pleura and a delicate layer of areolar and lymphatic tissue. On the left side there are 3 cm. or more of large blood vessels and esophagus plus areolar and lymphatic tissue interposed between the trachea and the apex (Figs. 1, 3, 4, 5 and 6). And to this difference I would ascribe the rationale of the variation in the normal sounds. Why assume that the vibrations in question must pass through a long and devious course, and to differences in this course on the two sides (differences shown to be of little importance in their ultimate result) ascribe the preponderance on the right side? The explanation I suggest is simple, perhaps obvious when once noted, and its principle is observed daily in diseased conditions. Is not whispered pectoriloquy transmitted to the ear from a tuberculous cavity through sound overlying pulmonary tissue? And is there any difference in principle between transmission from a cavity through healthy upper lobe and apex tissue? It does seem when these facts are taken into consideration and either the actual frozen sections or the appended illustrations studied, that the explanation offered is the rational one. And all that is needed to prove the truth of this contention is to find a patient in whom the right bronchus is plugged and no air is entering the right lung. If the theory advanced is correct, there will be found, in spite of the obstruction, vocal fremitus and vocal resonance at the right apex.

NOTE.—Acknowledgments are due to Dr. A. W. Goodspeed, Professor of Physics in the University of Pennsylvania, for valuable suggestions, and to Dr. P. G. Skillern, Jr., for assistance in preparing the specimens from which the illustrations were made.

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## MULTIPLE NEUROFIBROMATOSIS (VON RECKLING-HAUSEN'S DISEASE)

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The occurrence of isolated tumors of nerves is relatively frequent, probably more so than generally supposed, for the reason that in the case of many fibromata, fibromyxomata or other tumors a connection with nerves is not always ascertainable. Most tumors of nerves are fibromata or fibromyxomata. I have studied fourteen such tumors, eight of which were situated in the nerves of the forearm and five in those of the lower limbs. The cases were equally divided between the sexes. Most of the tumors occurred in patients between 20 and 40 years of age, and in some of the cases the tumors developed slowly, in the course of ten to fifteen years. In a woman of 50 years there first appeared a pure fibroma, which was removed by operation. Then repeated recurrent growths appeared which gradually became sarcomatous and caused death ten years after the appearance of the first tumor.

The tumors of the optic nerve, five of which were examined, form a separate group, as they possess both clinical and histologic peculiarities. They are most frequent in children. Four of our cases were in boys, 5, 8, 11 and 13 years old. The first symptoms generally are decrease in vision, pain and increasing exophthalmos. The latter may reach such an extreme degree that the eye actually hangs out of the orbit. The growth is usually rapid, though occasionally it is slow, as in two of our cases in which it required five and seven years respectively. The tumors are located in and on the optic nerve (Fig. 1), which presents a spindle-shaped enlargement tapering anteriorly and posteriorly. As a rule they are well circumscribed and do not infiltrate the eye or other surrounding structures. Metastases and recurrences generally do not occur, hence the tumors are relatively benign. Their histologic structure is difficult to interpret. Most often they have been looked upon as sarcomata with varying types of cells arising from the stroma of the optic nerve. In my opinion it is most probable that they are to be considered gliomata (Figs. 2 and 3), arising from the glia in which the optic nerve fibers are imbedded, and in that case they should be classed together with the retinal gliomata and be separated from the ordinary fibrous tumors of nerves.



The border between the isolated tumors of nerves and von Recklinghausen's disease is formed by cases of multiple neurofibromata without the existence of tumors or pigmentation of the skin or other abnormalities. I have had opportunity to examine two such cases in which re-

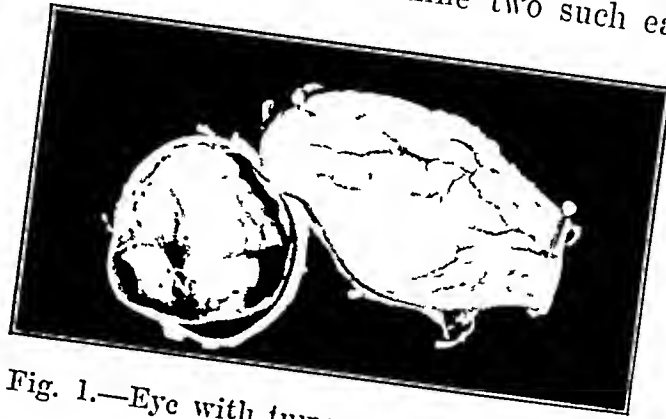


Fig. 1.—Eye with tumor of the optic nerve.

peated recurrences after extirpation took place, sometimes with short intervals, but the tendency to recurrence disappeared and evolution into sarcoma did not take place.

CASE A.—A man who at the age of 68 years died of apoplexy, at 45 developed multiple fibromata of the nerves of the left forearm, particularly the ulnar and median nerves and their branches. The tumors gradually caused so much pain



Fig. 2.—Cross-section of optic nerve with tumor. In the center the optic nerve surrounded and compressed by tumor masses.

that in his sixtieth year an operation was performed, when numerous sharply circumscribed tumors varying from the size of a pea to that of a walnut were removed. Recurrences took place a year later and about thirty similar tumors



were removed; a year after this forty or fifty tumors were removed, and finally, one and a half years later, a long, cord-like nerve swelling and several smaller growths were removed from the forearm. All these growths were found to be fibromata rich in cells. The patient then was free from recurrences and free from pain until his death. The family history was negative.

CASE B.—In a man who died at the age of 24 years from tuberculous small tender lumps in one forearm and hand had existed from early childhood. They were most numerous in the median nerve and to a considerable extent had undergone cystic degeneration. At the age of 17 years several of these tumors were extirpated on account of pain, and were found to be fibromata. After a little more than a year recurrence took place and several similar tumors were removed, but from that time on the patient was free from recurrences. In this case there was also no known heredity.



Fig. 3.—Cross-section of optic nerve infiltrated with tumor tissue. Optic nerve to the left; tumor tissue (probably glia tissue) to the right.

Both cases illustrate the tendency to rapid growth and to recurrence soon after operation.

Great interest is attached to those cases of multiple tumors of nerves which are accompanied by a series of other symptoms, showing that we are dealing with a general disease, or constitutional anomaly, if it be desirable to use that term. This is to be inferred, first, because the disease affects more or less extensive parts of the nervous system, hence is

a "system disease," although with variable clinical picture; second, because it is frequently accompanied by tumor formation, and especially pigmentation of the skin; further, because as secondary, less important and less frequent symptoms, we encounter a series of psychic, trophic and vasomotor phenomena. When, in addition to this, in about one-fifth of the cases we find an hereditary basis, the malady either appearing as a family disease or occurring in several generations, although in different forms, it must be admitted that this affection deserves to be



Fig. 4.—Patient 1.

recognized and borne in mind, especially as it is not as rare as might be supposed, particularly if the incomplete forms or *formes frustes* be included.

The disease has been known for a long time. In 1849 the gross anatomic characteristics were described by R. W. Smith.<sup>1</sup> Virchow<sup>2</sup>

1. Smith, R. W.: A Treatise on the Pathology, Diagnosis and Treatment of Neuroma, Dublin, 1849.

2. Virchow: Die krankhaften Geschwülste, 1863.

determined that the tumors originated from the connective tissue element of the nerves. The next advance is associated with the name of von Recklinghausen,<sup>3</sup> after whom the disease later was named. He showed that different forms which until then had been considered separate, really formed a histogenetic unit, especially as in cases of pronounced tumor formation in the skin the tumors were found to develop from the nerves. Later investigators have especially endeavored to establish and describe different types and to study the histologic struc-

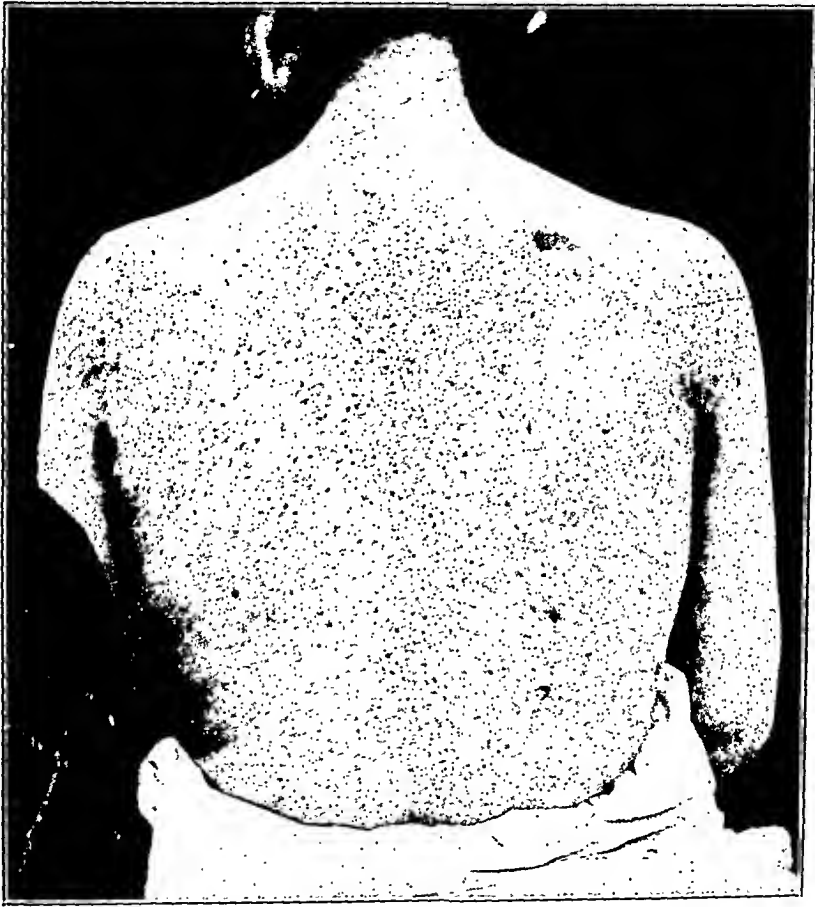


Fig. 5.—Patient 1.

ture. Among later works the monograph of Thomson<sup>4</sup> deserves special mention, and, so far as American literature is concerned, the articles of Prudden<sup>5</sup> and Hektoen and Preble.<sup>6</sup> As I recently had opportunity to

3. von Recklinghausen: Ueber die multiplen Fibromen der Haut und ihre Beziehung zu den multiplen Neuromen, 1882.

4. Thomson: On Neuroma and Neurofibromatosis, 1900.

5. Prudden: Am. Jour. Med. Sc., Phila., 1880, lxxx, 134.

6. Hektoen and Preble: Am. Jour. Med. Sc., Phila., 1901, cxxi, 1.

investigate both the clinical and anatomic details of a number of cases of neurofibromatosis of different types, I will first briefly relate the cases, and later in connection with them make some remarks with special reference to prognosis, symptomatology and histogenesis.<sup>7</sup>

CASE 1.—In a woman 52 years old when observed (Figs. 4 and 5), there had appeared when she was 26 years old, an eruption of fibromata on the chest, back, face, arms and legs. They were soft, not tender, varying in size up to that of a pea; they grew slowly. It was also found that she had numerous pigmented spots all over her body, but there were no tumors on the nerves. The tumors



Fig. 6.—Patient 2, daughter of Patient 1.

had the structures of fibroma. On inquiry about the family nothing hereditary was found, but it was learned that her daughter was similarly affected.

CASE 2.—(Fig. 6.) The 23-year-old daughter of the patient just described (CASE 1) had abundant pigmented spots, some of which were freckle-like, others large and light in color, scattered over the entire body. On the back she also had a red angiomatous area, a few soft fibromata and bluish-violet very soft superficial lumps, but there were no growths on the nerves.

7. Complete description of these cases will appear in *Norsk Mag. f. Lægevidensk.*, Christiania, 1909.

CASE 3.—A woman 36 years old (Fig. 7), of a healthy family, had multiple growths on the chest, back, arms and face, also a few bluish-violet, slightly raised soft patches, and on the left side of the chest a hard pedunculated fibroma of the size of a child's head, the upper surface of which was ulcerated. There were numerous pigmented spots but no tumors of the nerve trunks.

These three cases are instances of the simple form of von Recklinghausen's disease characterized by generally soft, though occasionally hard, cutaneous fibromata and by pigmentary anomalies.



Fig. 7.—Patient 3.

In the following cases there were also multiple neuromata of the subcutaneous nerves:

CASE 4.—A man 28 years old (Figs. 8 and 9) had numerous pigmented spots scattered on his trunk and limbs. These had existed from birth. The patient also had a large number of soft cutaneous fibromata which had developed after the age of 15 years. On the inside of the right arm were a few hard, tender, spindle-shaped, small fibromata situated on the nerves. On histologic examination of these (Fig. 10) most of the nerve fibers were found preserved as a central

bundle surrounded by proliferated connective tissue arising from endoneurium and perineurium. The only further congenital anomaly which was found was a cryptorchidism.

CASE 5.—A man 55 years old (Figs. 11 and 12), of small, almost dwarf-like stature, had extremely numerous soft cutaneous fibromata, most numerous on the trunk, decreasing in number along the arms and legs. The tumors were partly pedunculated, partly sessile and hemispherical, and reached the size of a walnut. They had been present since childhood but had gradually increased in number and in size. There were also numerous flat, closely placed, bean-sized nodules on the face. He had, moreover, large, brown, oval, pigmented areas and a few small,

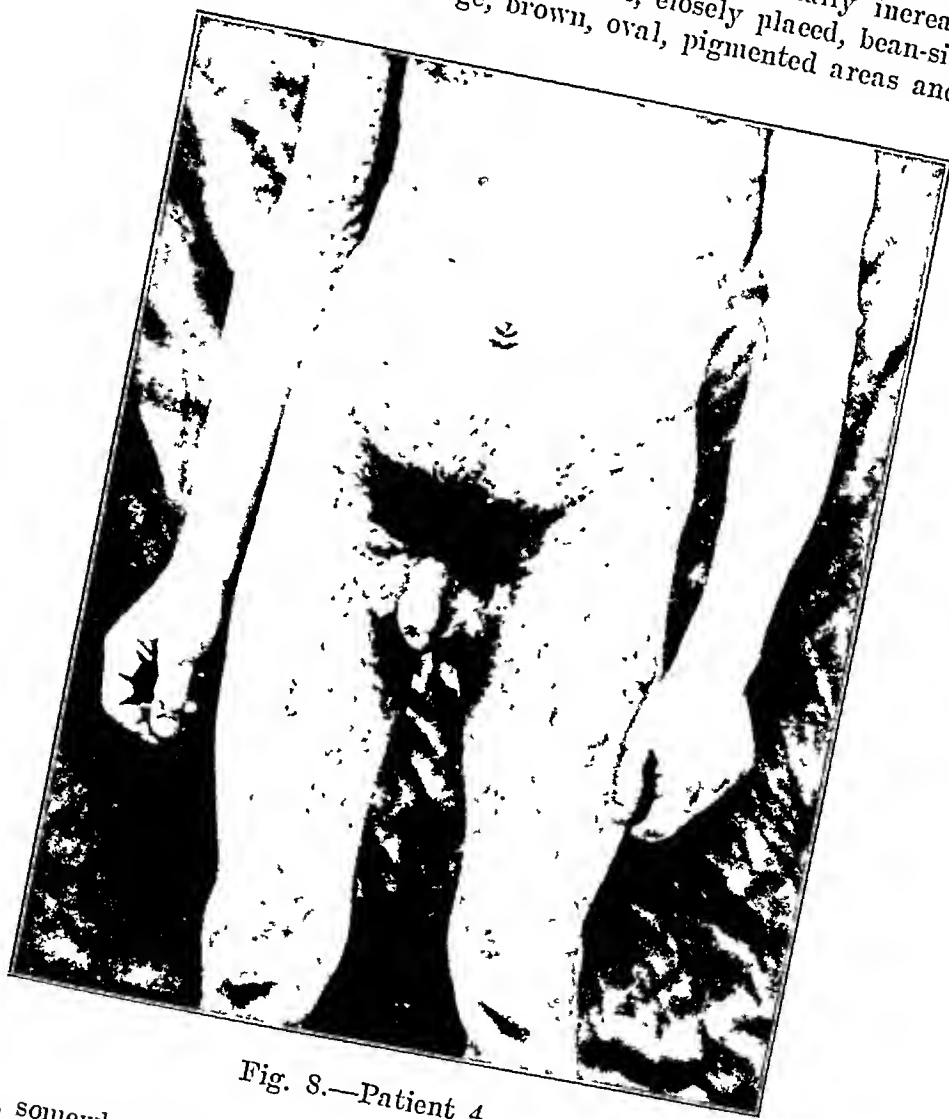


Fig. 8.—Patient 4.

spindle-shaped, somewhat tender nodules of the subcutaneous nerves on the inside of the arm. He gave the impression of possessing little intelligence. No similar cases were known to exist in the family.

CASE 6.—A woman 19 years old had a growth removed which was located in the upper eyelid and the left temple and found to be a racemose neuroma. (*Racemose neuroma*; Figs. 3 and 4.) This tumor had appeared in the course of the last two years. She also had scattered, soft, cutaneous fibromata and numerous small and large pigmented areas, said to have been congenital, as well as some areas devoid of pigment which were most numerous on the neck. On both sides of the neck, in the right axilla, and on the inside of the right arm there were a

few tender, spindle-shaped nodules on the nerve trunks. In the following four years, during which I had opportunity to observe her, a small recurrent growth appeared in the eyelid, and during a period of lactation there was an eruption of a large number of small fibromata on the subcutaneous nerves. There was no known heredity.

This case, then, is an example of coexisting racemose neuroma ("Rankenneurom") and subcutaneous neurofibromata in addition to soft fibromata and pigment anomalies of the skin. Judging from the course, the prognosis here was somewhat doubtful.

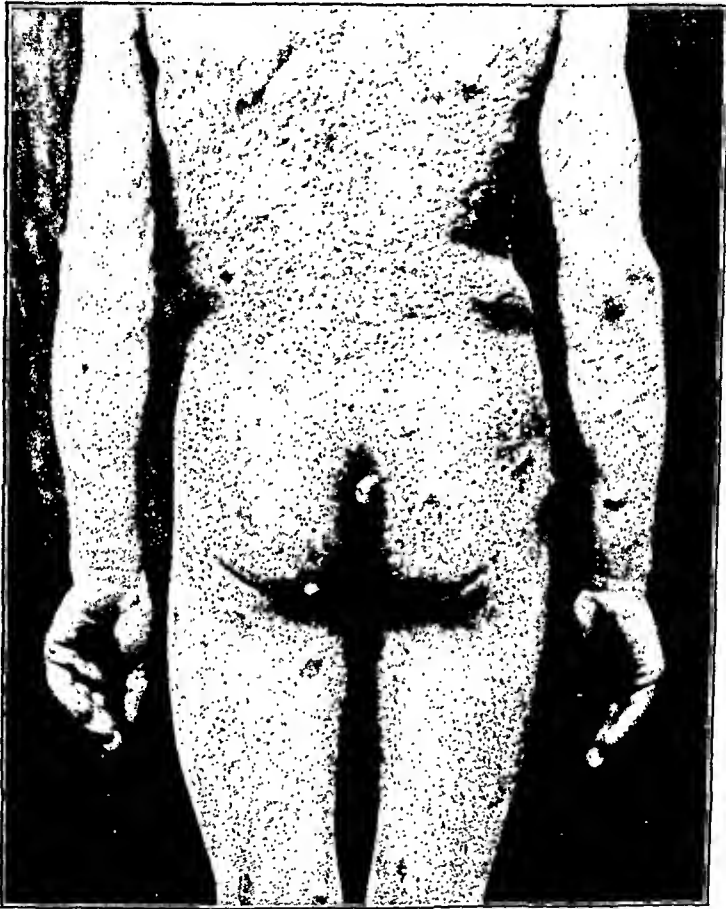


Fig. 9.—Patient 4.

The following three cases illustrate the addition of elephantiasis-like growths:

CASE 7.—In a woman 29 years old, of a healthy family, herself an imbecile of the Mongolian type (Figs. 16 and 17), there appeared, at the age of 6 or 7 years, a tumor on the back of the left thigh. This tumor later developed into a large elephantiasis-like growth of the thigh and external genitals of the left side. Later there also appeared numerous small fibromata on the trunk, face and, to some extent, on the extremities, as well as many pigmented areas. There were, however, no demonstrable nodules on the nerve trunks. She was, on the whole,

well built, but slender. The characteristic appearance of the face—oblique eyes far apart, narrow palpebral fissures, broad nose—did not exist from birth but developed at about the age of puberty.

CASE 8.—A man, 47 years old (Figs. 18 and 19), of a healthy family, had a congenital growth in the right upper eyelid which gradually spread to form a large, elephantiasis-like mass on the right side of the face, including the right side of the forehead and the right temple. At the age of 8 years it caused blindness in the right eye. At the age of 21 years extirpation was performed and after that time there was little growth. He was not aware of the existence of other tumors, but on examination a number of small fibromata were found on the chest and back and also numerous pigmented areas, some of them very large, chiefly in the *rima inter nates*, and on the hips and thighs, while a few tender string-shaped and spindle-shaped subcutaneous tumors of the nerves of the inside



Fig. 10.—Case 4.—Cross-section through a small tumor nodule on a subcutaneous nerve; in the center a large bundle of normal appearing nerve fibers in the periphery of proliferating connective tissue.

of the left arm were also detected. The man had a kyphosis which was said to have developed in childhood; it could not be determined whether this was the result of an old tuberculous spondylitis, or whether, as has been claimed in other cases, especially by French observers, the bone disease had some connection with the multiple neurofibromatosis.

CASE 9.—A woman, A. L., 25 years old, who died of erysipelas, had from birth a great fibromatous thickening constituting an actual elephantiasis of the entire left lower extremity (Fig. 20) and of the left side of the external genitals. The thickening had been slowly increasing. The circumference of the leg was 45 cm. and that of the thigh 72 cm. The thickening consisted of fibromatous prolifer-



ation of the cutis and the subcutaneous tissue, the combined thickness of which measured 3.5 to 4 cm. (Fig. 21.) The skin of the left leg was wrinkled, corrugated and shagreen-like. In addition, the skin of the right side of the back and right shoulder showed thickly set, greyish-white, in part very hard nodules; there were no subcutaneous neurofibromata. On the neck there were also leucodermoid areas resembling cicatrices.

A peculiar symptom to be noted was the occurrence, every two weeks since the age of 14, of attacks of trembling and chilliness, with subsequent sensation of heat and sweats. It was learned that similar elephantiasis of the lower ex-

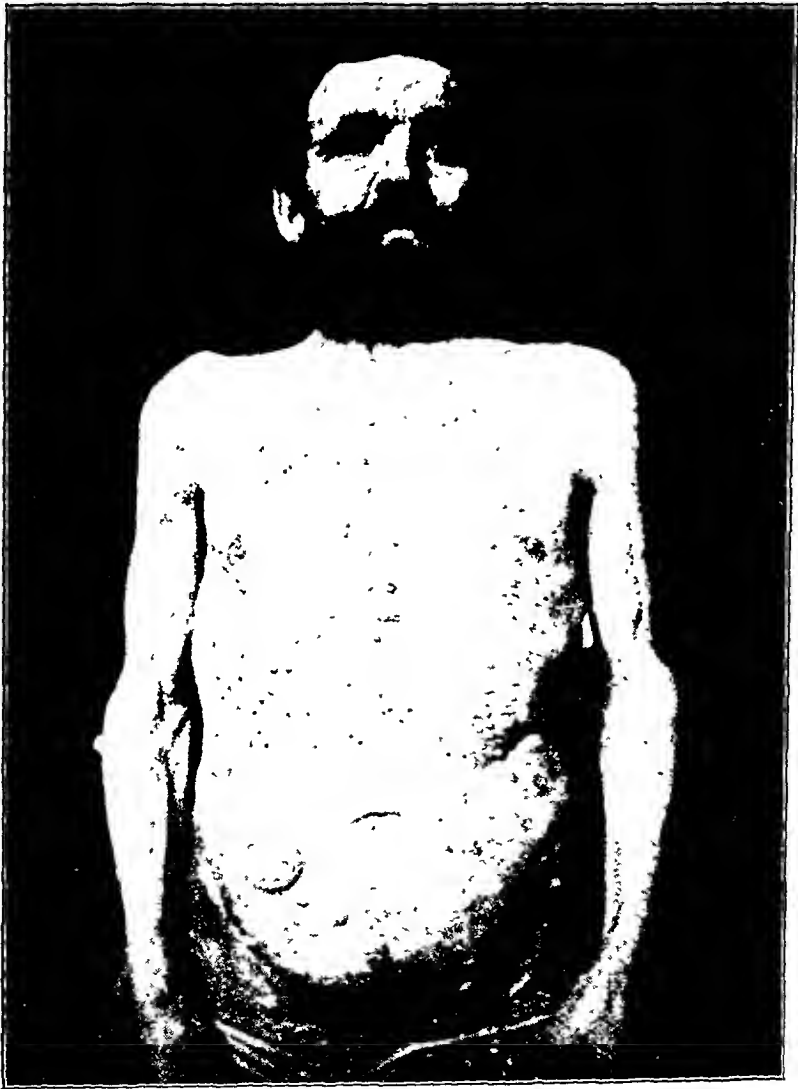
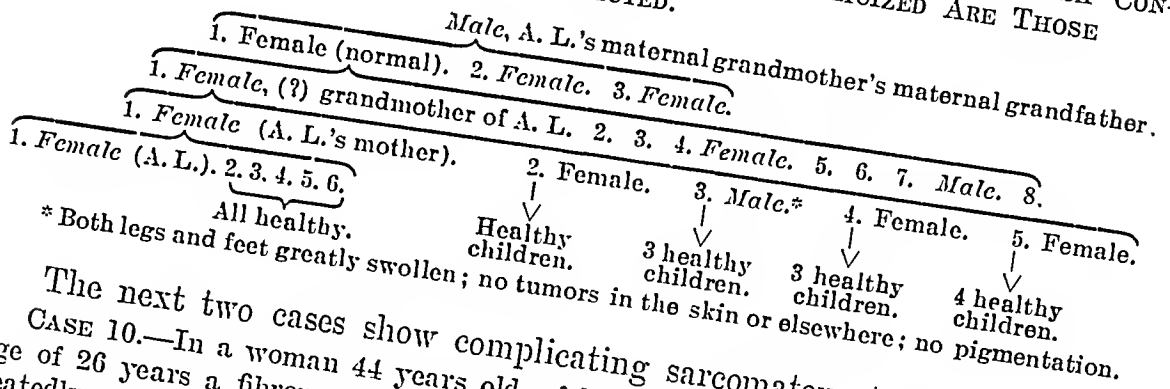


Fig. 11.—Patient 5.

trémities had existed in the four previous generations of the patient's family, often in several members of the same generation. The tendency to this condition was apparently chiefly transmitted through the female members of the family, the other cases having occurred in (1) the mother and mother's brother; (2) the maternal grandmother and her brother and sister; (3) two sisters of her great-grandmother; (4) the maternal grandfather of mother's mother. The family could not be traced farther back. For particulars see genealogical tree.

GENEALOGICAL TREE OF A. L. (CASE 9). ELEPHANTIASIS NEUROMATOSA CON-  
GENITA IN FIVE GENERATIONS. THE MEMBERS ITALICIZED ARE THOSE  
AFFLICTED.



The next two cases show complicating sarcomatous transformation: CASE 10.—In a woman 44 years old, of healthy family, there developed at the age of 26 years a fibroma of a nerve of the thigh which was extirpated but repeatedly recurred with the gradual formation of an infiltrating sarcoma of which she finally died, cachectic, at the age of 44. She had undergone ten operations in the course of eighteen years. She also had plexiform neuromata of the nerves of one thigh, multiple, circumscribed neuromata of the subcutaneous nerves of the trunk (Figs. 22 and 23) and numerous soft fibromata and pigmented areas of the skin, chiefly of the trunk.

All the cardinal symptoms of von Recklinghausen's disease were present. Of particular interest was the development of sarcoma in connection with a plexiform neuroma of the thigh (see also the following case).

CASE 11.—A woman 32 years old (Fig. 24), from early childhood had small tumors of the trunk. Gradually there appeared numerous soft and hard fibromata of the skin, particularly of the chest and back, and numerous pigmented areas. When she was 28 years old a tumor formed in the left sciatic nerve which was removed and found to be a plexiform neuroma (Figs. 25 and 26) of a large part of the sciatic nerve with pronounced gelatinous and colloid degeneration. Repeated recurrences took place and gradually the tumor assumed the character of an infiltrating sarcoma. Finally the whole sciatic nerve was transformed into a cord 4 to 5 cm. thick (Fig. 27) which adhered to the surrounding structures. On all the branches there were bean-sized, fusiform enlargements, with pronounced myxomatous degeneration. She died soon after leaving the hospital, presumably of recurrence.

CASE 12.—In a man 38 years old, who died of ileus, there were accidental necropsy findings of numerous yellowish-brown pigmented areas of the chest, back and neck, most of which were of pin-head size, others of the size of beans, and a few oval and very large areas on the lower part of the back and on the thighs (the largest measured 2 x 5 cm.). Scattered on the trunk and arms there were numerous small soft fibromata, the overlying skin of which was white and unpigmented and partly covered with long hairs. They were most numerous on the chest and back. There was a soft, very prominent nodule of the size of a pigeon's egg on the right shoulder. There were no distinct nodules on the nerves, of which the brachial plexus, pneumogastric and sympathetic nerves were dissected out. The tumors showed the structure of a fibroma rich in cells.

CASE 13.—In a woman 55 years old who died of an abdominal tumor the necropsy revealed: 1. Soft, freely movable cutaneous and subcutaneous tumors from the size of a pea to that of a nut. 2. Numerous thickly set brownish

spots on the abdomen and both thighs of the size of hemp-seeds, alternating with pigment free areas. There was also a carcinoma of the left ovary, with secondary infiltration of the omentum and extension to the peritoneum and pleuræ. Finally, there was in the mesentery a large nodular tumor mass with extensive central necrosis and softening of large portions. Microscopically this tumor was found to consist of large, spindle-shaped cells separated by scant intercellular substance, and large irregular cells with large nuclei rich in chromatin—on the whole, a decided sarcomatous structure. On the other hand, the ovarian and omental tumors



Fig. 12.—Patient 5.

showed distinct carcinomatous structure with cells of epithelial character arranged in distinct clusters, some of which possessed central lumina.

In this case we then had a combination of carcinoma, sarcoma and multiple soft fibromata of the skin.

CASE 14.—An unmarried woman 51½ years old had had nodules on the trunk from birth. At the necropsy numerous nodules from the size of a bean to that of

a nutmeg were found scattered over the entire trunk, especially on the chest, and also numerous, very small, in part scarcely visible, nodules covered by soft, smooth, as a rule non-pigmented skin. The largest were located on and about the areolæ of the mammae. On the chest there were 200 or 250 nodules, while those on the back were less numerous, but larger. On the neck there were some nodules of the size of a pea; a very few were found on the extremities. Several pigmented areas for the most part of the size of a hemp-seed, but also a few large ones, were present on the skin, especially that of the abdomen. She had also suffered for about fifteen years from a chronic disease of the larynx, probably tuberculous. About six months before the patient's death a carcinoma of the larynx and tongue developed and gradually formed a large infiltrating tumor. No changes were found in the central nervous system, spinal ganglia, vagi, sym-



Fig. 13.—Patient 6. Plexiform neuroma in the left temple and left upper eye lid.

pathetics, cervical plexus, or sciatic nerves and their branches. There was no demonstrable family history as far as the occurrence of tumors was concerned.

CASE 15.—The following very peculiar case of "elephantiasis congenita" is included, although it is very doubtful whether we are here really dealing with an instance of von Recklinghausen's disease. It is that of a new-born infant, now an old specimen in the Museum of the Pathologic Institute of Christiania. Both parents had been healthy and had four other healthy children. This child, which was born at full term, had lived thirty-six hours. It cried and nursed well. The cause of death was a left-sided pneumonia.

The appearance of the child (Fig. 28) is very peculiar, first suggesting lepra nodosa with the facies leonina. It is of the size of a full term child, being

49 cm. long and weighing about seven pounds. On the whole, it is well proportioned, although the arms are rather long as compared to the trunk. The most conspicuous features are a peculiar thickening and numerous flat prominent nodules of the skin. The skin has the appearance of being too large, with the formation of folds, especially on the extremities. On the arms and legs there are numerous transverse wrinkles and grooves separated by thick folds of skin. This is also very pronounced on the whole head and especially on the face, which for this reason has a peculiarly gruff expression. The eyes almost disappear in deep furrows between swollen eyelids, and the nose and ears look like nodular tumor masses.

The thinnest and smoothest part of the skin is that of the trunk, but here also small nodules are seen in the form of numerous scattered, fairly well circumscribed, small infiltrations. The nodules are most thickly set on the extremities, on the legs and in the palms, where they vary from the size of a hemp-seed to that of a bean. The skin is also diffusely infiltrated over large areas. On incision of the nodular and thickened portions the thickening is found to be in the cutis and to measure as much as 1 cm.

The internal organs were found to be normal. Nothing was found in connection with the central or peripheral nervous systems. Microscopically, sections



Fig. 14.—Case 6.—Plexiform neuroma. The white nerves with nodules have been dissected apart.

from various parts of the infiltrated skin presented the same picture, namely, diffuse infiltration with numerous small, closely placed cells throughout the cutis and penetrating into the subcutaneous tissue. The cells are small, polygonal or round, with distinct, deeply stained nuclei and abundant cytoplasm. The border of the infiltrations is diffuse, especially in the subcutaneous tissue. Any origin from the nerves could not be demonstrated.

*Epicrisis.*—The histologic picture is most likely to be explained as tumor formation, resembling round-celled sarcoma or mycosis fungoides, but it also bears considerable resemblance to a granuloma.

#### THE ANATOMIC CHARACTER OF THE DISEASE

From the description of the cases (and from the illustrations) it will be seen that the essential symptoms of multiple neurofibromatosis are: multiple cutaneous tumors, pigment anomalies, tumors of nerves in their various forms, and elephantiasis-like formations.

The most frequent and almost constant change observed is the presence of multiple tumors of the skin, the so-called mollusea fibrosa, which were found in all of our cases, though exceedingly variable in extent and size. Sometimes they are found by the hundred or thousand (Cases 4 and 14). The size varies from the very smallest point to that of a hazelnut or hen's egg; sometimes they cause trouble by their size; ulceration may necessitate removal by operation (Case 3). They are most numerous on the trunk and particularly in places subject to mechanical pres-

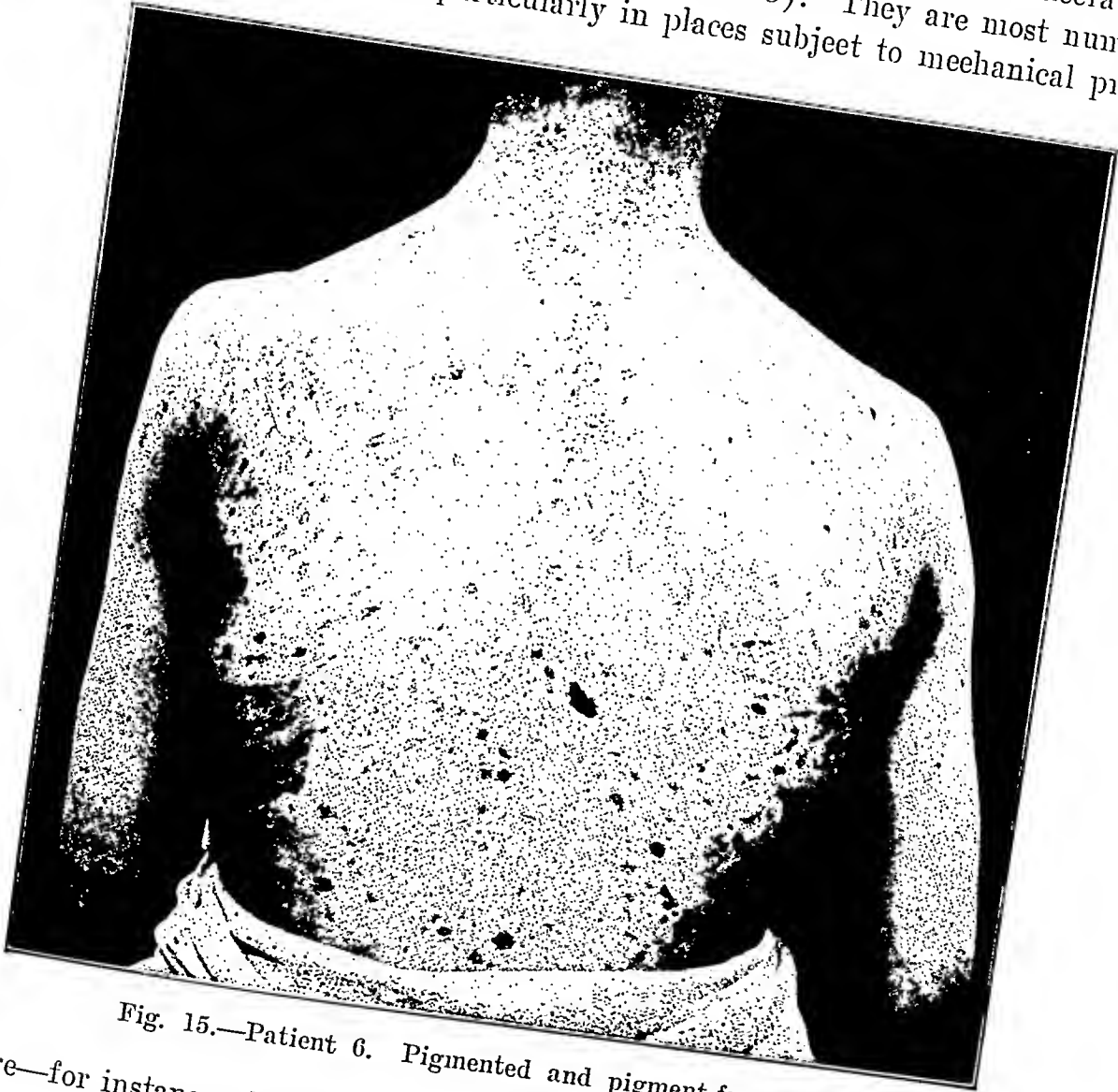


Fig. 15.—Patient 6. Pigmented and pigment-free spots.

sure—for instance, about the waist. They are also relatively frequent on the neck, head and hips, but less so on the extremities. They are generally soft, freely movable, not tender, and are partly located on the skin, partly in the deep portion of the cutis or in the subcutaneous connective tissue. When they are recent and in active growth they often appear as bluish-red or violet flat nodules or indistinct infiltrations in the skin, consisting of soft, edematous connective tissue poor in cells; later, when

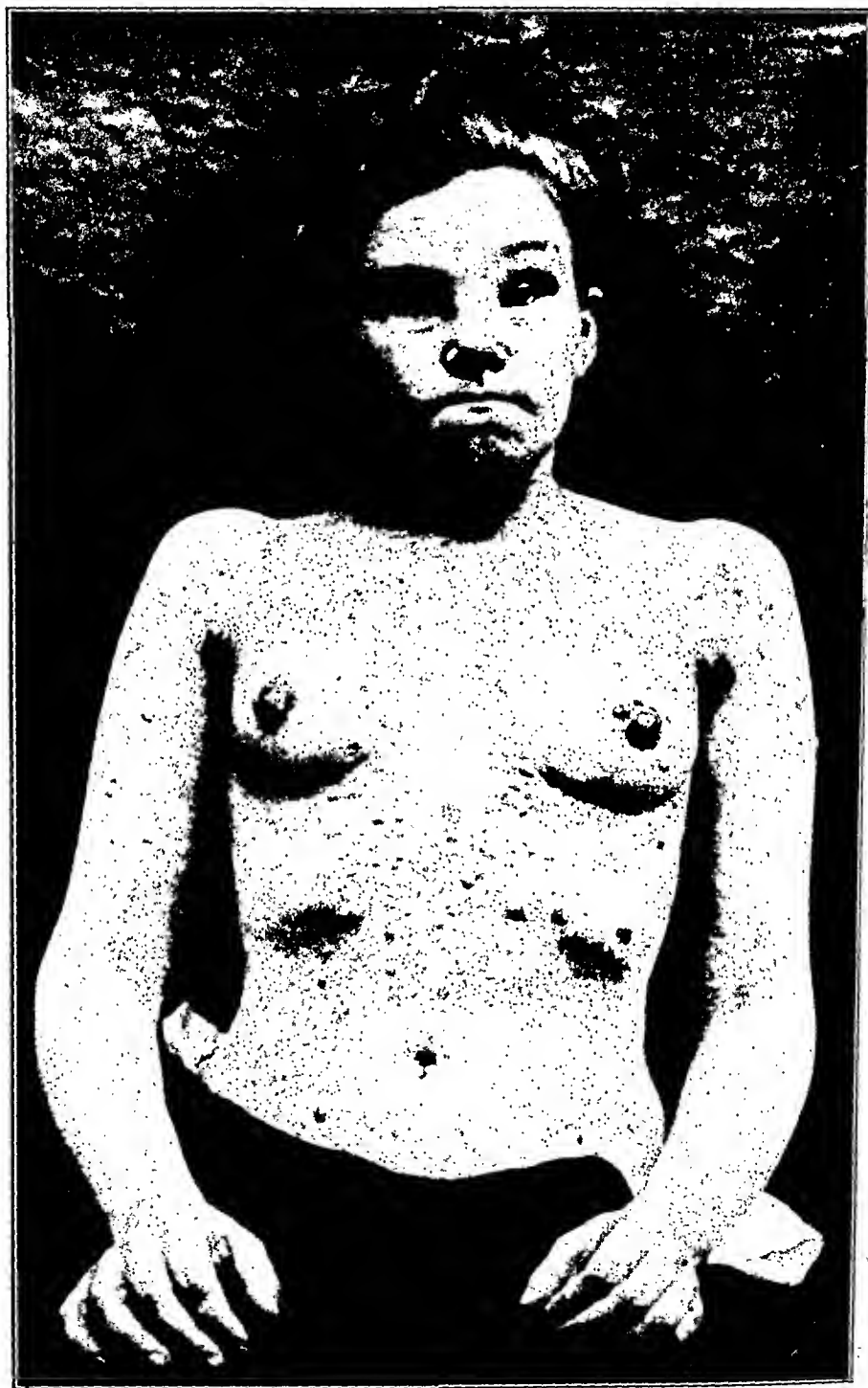


Fig. 16.—Patient 7.

fully developed, this connective tissue is often rather rich in cells. As a rule these tumors are very irregularly distributed over the skin and show no distribution corresponding to that of nerves.

At the same time one also sometimes finds tumors in the larger branches of nerves located in the subcutaneous tissue and deeper (for



Fig. 17.—Patient 7.

instance, Cases 4, 6, 10 and Fig. 22). They are most frequently found in the nerves of the extremities, as, for instance, on branches of the ulnar, median or sciatic, but are also seen on the intercostal, pneumogastric, sympathetic and other nerves. They are generally somewhat tender so



that pressure produces radiating pains. They are spindle-shaped, movable from side to side, but as a rule not from above downward. They generally cause trouble only by their location and size. Curiously enough functional disturbances are comparatively rare, especially motor phenomena; occasionally, however, sensory disturbances are encountered.



Fig. 18.—Patient 8.

The rarity of these disturbances is due to the fact that the nerve fibers in the tumors persist a long time without degenerating. If they are removed, functional disturbance is as a rule absent, possibly because other nerves have taken up their function.

But the tumor infiltration of the nerves may also show itself in different forms, namely: as diffuse infiltration, diffuse fibromatosis of one or several nerves or of a nerve plexus. The infiltrated nerves then appear as swollen, cylindrical or nodular, tortuous and branching cords, grayish-white in color and as a rule firm in consistency. This condition is spoken of as plexiform neuroma (Figs. 25, 26 and 27), especially where connection with nerves or a plexus is readily demonstrable (Cases 10 and 11). A bundle of racemose nodular masses which form a more isolated tumor



Fig. 19.—Patient 8.

with a single pedicle and without intimate connection with nerve trunks or a plexus we designate racemose neuroma or "Rankenneurom" (von Bruns) (Figs. 13 and 14). The extension here chiefly occurs in width and thickness. This form of tumor has certain favorite locations, such as the orbit and eyelids (Case 6), more frequently the upper lid (43 out of 79 cases), the temples, the region of the ears (12 out of 79 cases), the back of the neck and occiput—in general the locations which are the

favorite seats of certain forms of elephantiasis. The ordinary plexiform neuromata have other frequent locations, such as the nerves of the extremities, particularly the sciatic nerve and its branches, the vagi, sympathetics, etc.

The nerves sometimes are greatly swollen (Case 11) with simultaneous mucoid or colloid degeneration and form thick branching cords up to 1 cm. in thickness, or rather tubular formations with mucoid, thin contents (Figs. 25 and 27). In such cases it is not rare for secondary sarcomatous tumors to develop.

Strangely enough pathologic changes in the central nervous system are rarely found in association with these tumors of the nerves.

A peculiar and very interesting form of von Recklinghausen's disease is constituted by the elephantiasis-like conditions occasionally met with,



Fig. 20.—Patient 9. Congenital elephantiasis of left lower extremity.

the so-called elephantiasis neuromatosa (or pachydermatocele). This may depend upon a racemose neuroma (*Ranckenneurom*) or a large tumor in the skin or a nerve being covered by thickened skin; or we may find a more diffuse thickening of the skin and underlying parts of so great an extent that real deformities result, for instance, elephantiasis of the feet (Figs. 20 and 21). The latter form constitutes the true elephantiasis neuromatosa. The most frequent locations are the feet, legs, hips, external genitals, neck and face. As excellent examples we have Case 7, elephantiasis of the thigh; Case 8, of the face; and especially Case 9, with involvement of a whole lower extremity with pronounced hereditary tendency (elephantiasis in five generations). This form is generally con-

genital, or at least appears in early childhood, and usually has a very slow, painless evolution. The skin over such thickened portions is generally hard, uneven, rough (like shagreen), often arranged in folds like a ruff or ruche. At the same time we often find multiple tumors of the



Fig. 21.—To the left. Cross-section through the thickened skin on the left leg of Patient 9, natural size; to the right for comparison, cross-section through normal skin.

skin and nerves and pigment anomalies. Case 15 is included as an “elephantiasis-like” case, a counterpart of which I have not discovered in the literature. It is, however, very doubtful what we here have before

us. The thickening of the skin did not show any fibromatous structure and no connection was to be made out with thickened and infiltrated nerve trunks.

Another pathologic finding frequently encountered in multiple neurofibromatosis is abnormal pigmentation. It is generally said to be present in 25 per cent. of all cases. This figure does not correspond with our experience, as pigment anomalies were found in all of our cases. At any rate they form a characteristic feature of the whole disease, not a mere coincidence. The pigmentation may be congenital (Cases 4 and 7) in the form of scattered small brown spots or *naevi*, or the discoloration is more diffuse. Frequently, however, the spots develop later in life and increase in number, size and intensity of color. They may be punctate, freckle-like and then they are often exceedingly numerous; or the pig-



Fig. 22.—Plexiform fibroma of nerve (Case 10), natural size.

ment may collect in large areas or more circumscribed patches which are then generally of a lighter, chocolate color. The shape is most frequently oval, but may be exceedingly irregular. It is very rare to observe a localization corresponding to the distribution of certain nerves or a metamerie distribution. It was not found in any of our cases. In the absence of pigmented areas the skin is often found to be very dark with a diffuse brownish pigmentation. The pigmented spots are also most abundant on the trunk, neck and face, but there is no demonstrable direct connection between the spots and the tumors of skin or nerves.

Sometimes spots or patches free from pigment are seen to alternate with the pigmented ones. Occasionally one also finds angiomas of the

skin (Case 2), and this is sufficiently frequent not to be considered mere accident but a true feature of the disease. It should be remembered that certain forms of angioma, especially the so-called angioma arteriale racemosum, are frequently found together with pigmented naevi, or diffusely pigmented skin showing fibromatous thickening. It is more doubtful to what extent the rare cases of congenital multiple nodular angiomata are connected with or related to von Recklinghausen's disease. In a rare case of this sort in a 7-year-old boy with multiple tumors of the left hand

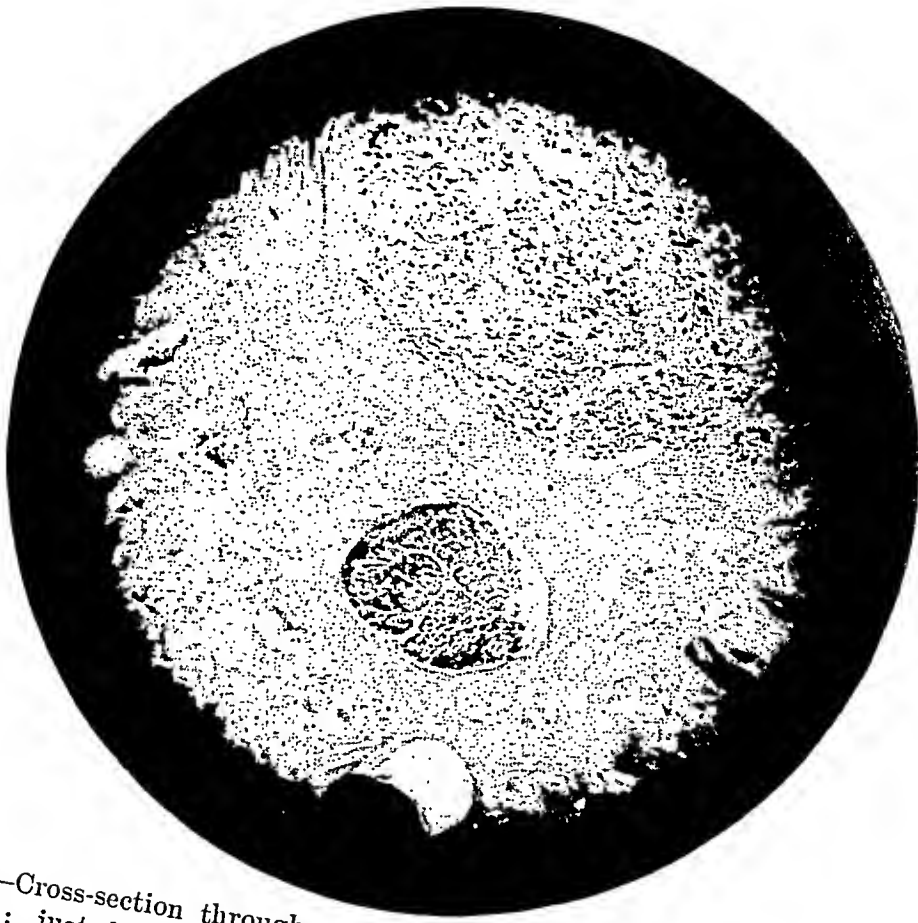


Fig. 23.—Cross-section through a small subcutaneous "neurofibroma" (micro-photograph); just below the center, cross-section of a nearly normal nerve bundle; in the upper part, cross-section through a nerve bundle in which the fibers are forced apart by the proliferation endoneurium from which the tumor originates.

and forearm whom I had occasion to examine a few years ago there were none of the cardinal symptoms of von Recklinghausen's disease.

It must be stated that all the phenomena described are not always found together. Most constant according to our experience are the fibromata and pigmented spots of the skin, while the tumors of larger nerves are less frequent. The elephantiasis-like conditions are still more uncom-

mon. As to other necropsy findings, the organs are usually found to be normal aside from congenital malformations which are occasionally met with.

#### OTHER SYMPTOMS

Aside from the "cardinal symptoms" one also finds in von Recklinghausen's disease a series of other "secondary symptoms" ("of the second order"), which are less reliable, as it is difficult to prove their actual connection with this disease. Here belong a series of psychic abnormalities which are encountered with relative frequency. The subjects are often

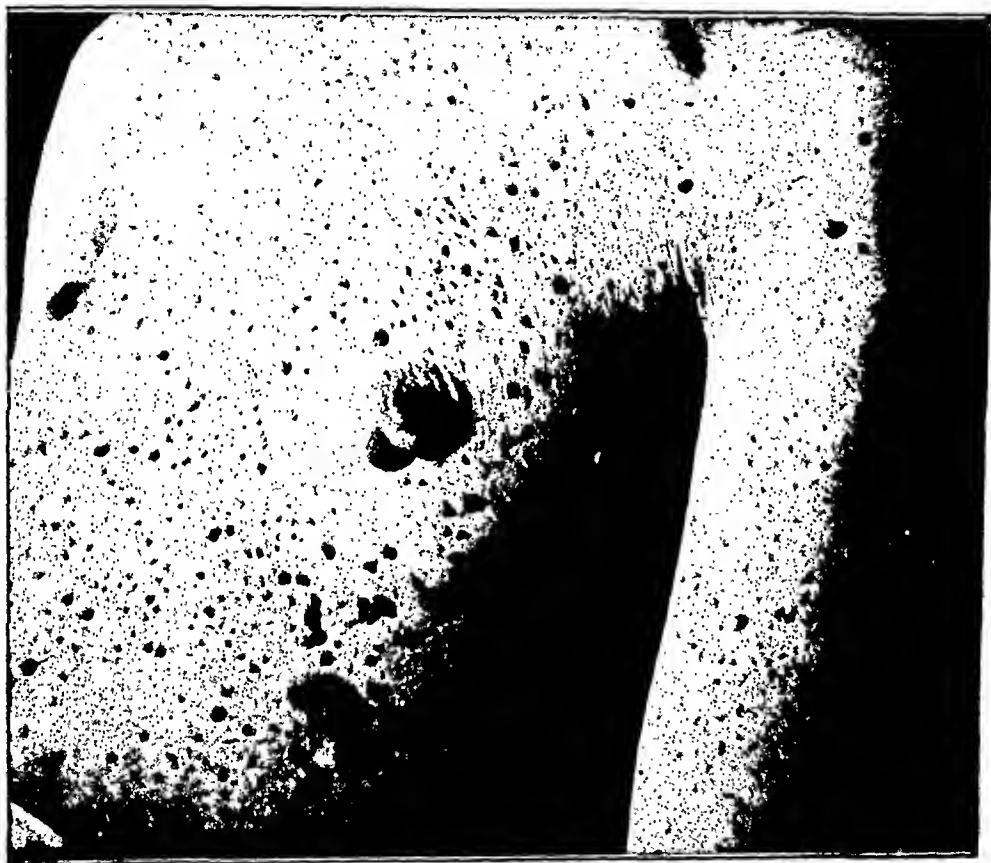


Fig. 24.—Patient 11.

dull and apathetic, of limited intelligence, or actually stupid, imbecile or idiotic. A striking example of such an imbecile of the Mongolian type is our Case 7. Congenital defects and malformations are not very rare, such as cranial defect, malformations of fingers, toes, cryptorchidism (Case 4), etc. The entire skeleton may be imperfectly developed with the appearance of nanism or cretinism. Such abnormalities are sufficiently frequent to be looked upon as symptoms of or links in the disease itself.

More doubt is attached to a series of vasomotor and trophic phenomena occasionally met with, such as certain peculiar joint affections, arthralgias and even arthritis deformans,<sup>8</sup> local asphyxia, peculiar attacks of unconsciousness, attacks of dizziness and cramps. Of doubtful connection are also certain osseous changes, such as a kyphoscoliosis of rapid formation (Case 8) which have been considered in connection with this disease as an expression of general cachexia, which in turn should depend on multiple neurofibromatosis (Pierre Marie, Hoisnard).

A peculiar symptom probably belonging to the disease was observed in our Case 9 (that of a woman 25 years old with elephantiasis congenita of pronounced hereditary basis), namely, for many years the regular occurrence of chills with subsequent sensation of heat and discomfort so that she was often confined to bed for one or two days at a time. Similar cases have been described by Bryk, Esmarch and Kulenkampff. It is also of a certain interest that we not rarely meet with menstrual disturbances, either total absence or late appearance of the menses.

However, such secondary phenomena are often entirely lacking. When present they are of great interest, especially in cases in which the disease otherwise presents only one or a few of the cardinal symptoms, so-called incomplete forms or *formes frustes* which are relatively frequent and the true nature of which is more readily recognized when they occur in families in which there are pronounced cases of von Recklinghausen's disease.

#### ETIOLOGY AND EVOLUTION.

The disease occurs at all ages and in both sexes but apparently with greater frequency in men. According to the most extensive statistics 65 per cent. of all cases are in men. This does not correspond with our experience, as of our fourteen cases ten were in women and four in men; our figures are, however, obviously too small to admit of conclusions.

Hereditary disposition is not infrequently demonstrable on one or the other side of the family; this has been observed in about one-fifth of all cases. The disease may appear in several brothers and sisters, or it may have occurred through several generations, and not uncommonly in different forms in different generations. "La neuro-fibromatose généralisée est congénitale toujours, héréditaire souvent et quelquefois familiale" (Feindel). Among our cases the disease was found in mother and daughter (Cases 1 and 2). Particularly interesting is Case 9 with

8. In the interesting case of Hektoen and Preble (Am. Jour. Med. Sc., 1901, cxxi, 1) there were, in addition to multiple tumors of cerebrospinal and sympathetic nerves, a polyarthritis deformans, kyphoscoliosis with ankyloses and contractures, and decubitus (mal perforans) and gangrene of one foot.



congenital elephantiasis in five generations, a unique or at least extremely rare observation. Nonne<sup>9</sup> has reported elephantiasis of the feet in eight members of the same family in three generations.

The disease, or at least some of its symptoms, may be congenital. This is particularly true of cases of elephantiasis (Cases 8 and 9). Tumors of the skin have also been observed from birth (Cases 11 and 14) but more often appear later. Congenital tumors of the nerves—multiple or isolated—have not been observed as far as known, although it certainly may be taken for granted that they have a congenital *anlage*. They sometimes are discovered in childhood (Case 6 and Case B), more often at the age of puberty, but also frequently at the ages of 40, 50 or 60, when prolonged latency must be assumed, as the tendency is congenital. As has been stated, the pigmentations may be congenital.

The evolution of the disease varies, but as a rule it is very slow, requiring many years. Most patients die with the disease, not from it. Ordinarily tumors and pigment spots in the skin begin to appear in small numbers; later new eruptions occur, often separated by intervals; at a more advanced stage tumors in nerve trunks and large cutaneous tumors appear. At a mature age the picture is usually very pronounced with numerous large tumors and extensive pigmentation. This is illustrated in our Cases 1, 2, 3, 4 and 6. The eruption of new nodules and pigmented areas is sometimes, though rarely, arrested. On the other hand, the fibromata of nerves often cease to grow after having broken out in large numbers, and sometimes even after repeated recurrences after operations new nodules cease to appear, the disease having become stationary (see the two cases, A and B, described in the beginning of this article). A large elephantiasis-like growth may develop slowly and steadily for years, then cease growing and become stationary (Case 8).

External influences appear as a rule to exert little influence, though in certain cases the disease seems to have a predilection for places where traumatic insults may be operative. It has also been thought that cold and moisture may call forth new eruptions or hasten their development; likewise chronic irritative conditions of the skin, bad hygienic conditions, mental suffering; all this, however, is very uncertain. But there is reliable evidence that intercurrent infectious diseases and intoxications may have such influence. Experience has shown more rapid progress of the disease especially during certain physiologic periods, such as puberty, menopause, pregnancy, puerperium, lactation (see Case 6).

Of great practical importance is the malignant metamorphosis of the tumors and especially the influence of surgical intervention in the course

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9. Nonne: Virchow's Arch. f. path. Anat. [etc.] Berl., cxxv.

of the disease. In this respect the different forms behave very differently, an important fact to know both in connection with prognosis and treatment. Removal of the ordinary soft fibromata only comes into consideration when they cause annoyance by their location or size; they are readily removed and do not tend to recur. The same is true of the ordinary slowly developing forms of elephantiasis, which as a rule do not recur. The racemose neuromata (*Rankenneuromen*) also develop rather slowly

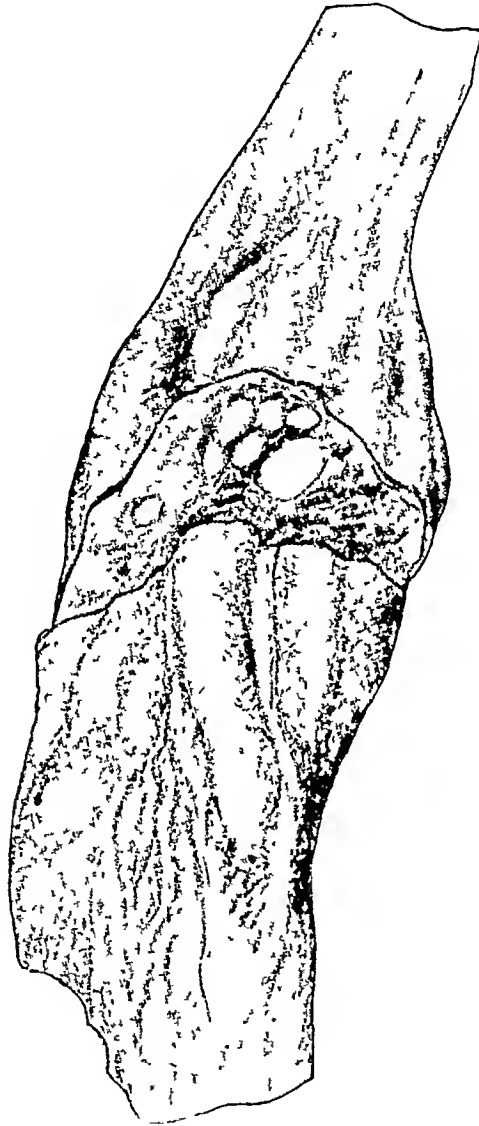


Fig. 25.—Drawing of a part of the plexiform neuroma of the sciatic nerve (Case 11). Here the tumor consists of a bundle of greatly thickened nerve fibers infiltrated with tumor tissue and matted together. On the cut surface are some of the thickened fibers that have undergone myxomatous and colloid degeneration.

and have a good prognosis; operative intervention does not seem to have an unfavorable influence on them. Our Case 6, however, seems doubtful in this respect.

The multiple deep-seated fibromata of nerves are also often removed with permanent cure, but in other cases rapid recurrence takes place. Even then, however, experience has shown that the disease may finally be arrested without further recurrence and without development into sarcoma (our first two cases, A and B, are good examples), but sarcomata have been known to develop, though slowly and after the elapse of many years (Case 10). Most caution as to prognosis is necessary in the case of ordinary plexiform neuromata, as development into sarcoma here is

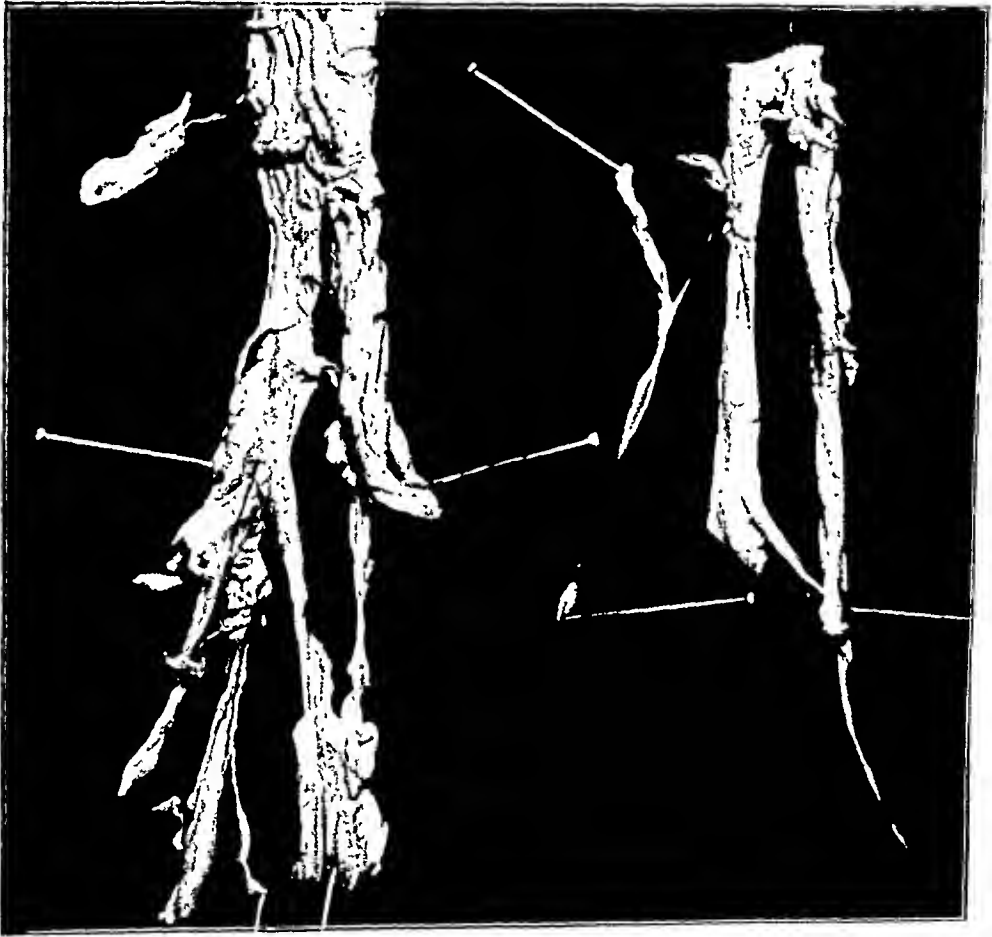


Fig. 26.—Plexiform neuroma in the sciatic nerve and its branches (Case 11).

not rare and sometimes operative intervention apparently hastens this development (see Cases 10 and 11), which has been given the undesirable name of "malignant degeneration;" the result is a rapidly growing infiltrating sarcoma. In many such cases it can not be denied that extirpation has had an injurious influence. There is rapid recurrence at the site of operation or diffuse eruption of nodules over large portions of the nerve plexus. Caution, therefore, is advisable in attacking these tumors

surgically, and if operation be performed the nerves affected should be extirpated to the greatest possible extent; in the case of sarcoma amputation ought to be performed (Thomson). Such evolution in the direction of malignancy is not rare. If all forms are considered it occurs in about 12.5 per cent. of the cases.

It is an interesting fact in connection with these growths that the simultaneous occurrence of other tumors is not unusual; such tumors may be benign or, more commonly, malignant, carcinomata or sarcomata, of external or internal organs. Our Cases 13 and 14 are good illustrations of this, Case 13 being especially noteworthy on account of the existence of both sarcoma and carcinoma. The relationship of these tumors at present is inexplicable, but their coexistence in these cases can not be looked upon as mere coincidence, and it appears justifiable to assume a

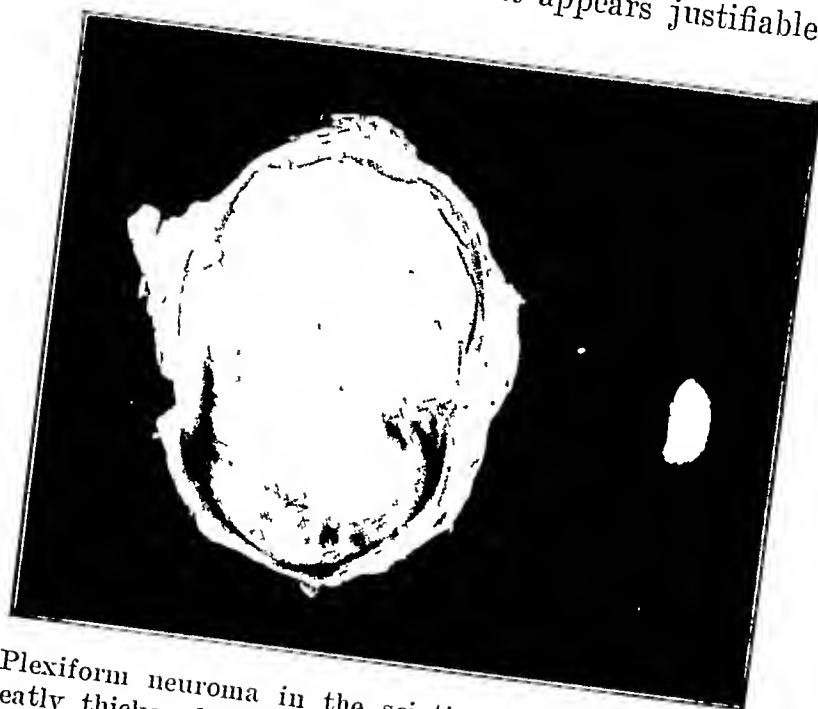


Fig. 27.—Plexiform neuroma in the sciatic nerve (Case 11). Cross-section through a greatly thickened and infiltrated nerve (to the left); to the right, cross-section of a normal sciatic nerve for comparison.

common disposition to formation of different growths. In this connection one is also naturally reminded of recent cancer experimentation in which, for instance, on transplantation of mouse carcinoma a sarcoma gradually may be evolved.

Is spontaneous recovery possible in multiple neurofibromatosis? Definite instances are scarcely known. It is not rare, however, for some nodules to disappear spontaneously, though it is hardly probable that subsidence of all the phenomena of the disease has been observed. That the disease may become stationary is an entirely different matter.

I do, however, know of one case of probable multiple neurofibromatosis (occurring in Christiania) in which spontaneous recovery has, apparently, taken place. A man of 70 years, still living, between the ages of 30 and 35 had several eruptions of cutaneous nodules on the arms, legs and shoulders. The nodules were soft, not tender, of pea to walnut size, and were thought to have been multiple sarcomata, a diagnosis which had been confirmed by four professors of medicine who successively examined the patient. An extirpated nodule was said to have shown sarcomatous structure and an unfavorable prognosis was made. The patient went to Kreuznach in two successive years to take the baths, and to the surprise of himself and his physicians all the nodules gradually and completely disappeared. When I examined him in February, 1908, there were no nodules to be found in the skin or nerve trunks, but there were several pigmented areas in the skin, some of which were rather large. The exact nature of this case can not be definitely determined, but it does not seem improbable that the nodules were neurofibromata of the skin and nerves.

#### PATHOLOGIC HISTOLOGY

Extensive microscopic examination of extirpated nodules of skin and nerves and pigment areas has been made in nearly all cases described, and on several occasions in cases where repeated operations had to be performed. In this way it has been confirmed that the tumors of the skin develop from the small cutaneous nerves and not from the connective tissue surrounding glands, vessels, etc., as has been supposed, among others by von Recklinghausen. It has further been found (Cases 10 and 13) that the tumors both of the cutaneous and larger subcutaneous nerves arise from the connective tissue portions of the nerves, their endo- and perineurium, and thus are to be looked upon as typical fibromata—which is in accord with general opinion. Most of the tumors are sufficiently characteristic to be recognized as fibromata, but not infrequently there is such abundance of cells that one may be in doubt as to whether the tumors may not be atypical and malignant; there are some cases in which it is very difficult, from the structure of the tumors alone, to form a conclusion as to their nature. The decidedly atypical tumors appear like ordinary spindle-celled sarcoma (sometimes giant-celled sarcoma), but transitional forms which are encountered in the case of slowly growing and recurring tumors are very difficult to interpret. The transition into malignant tumors also is as a rule very gradual, and the histologic pictures correspond to this; hence these growths also illustrate the fact that no sharp line can be drawn between benign and malignant, typical and atypical tumors.

The question has been raised whether these tumors of nerves could possibly be due to a proliferation of the sheaths of Schwann, the cells of which are now generally supposed to arise from neuroblasts and to be of



Fig. 28.—Subject in Case 15.

ectodermal origin. In this case the tumors would be more nearly related to gliomata. No evidence has, however, been produced in favor of this view, such as the occurrence of larger, more homogenous, embryonal cells,

signs of abundant nuclear proliferation, syncytial bands analogons to those seen in regeneration of nerve fibers or intracellular differentiation with formation of nerve fibers. Nothing of this kind is found. We see only ordinary fibrous tissue with intercellular substance, and it is scarcely probable that the cells of the sheath of Schwann, if they really are neuroblasts, should be able to produce ordinary connective tissue. It, therefore, appears incorrect to regard this disease as ectodermal, as do some French authors.

The racemose neuromata (*Rankenneuromen*) and the ordinary plexiform neuromata have the same evolution. In the cases of elephantiasis described it was also possible with more or less certainty to prove the origin of the thickening from the connective tissue of the nerves, but no proliferation of the connective tissue of vessels or cutaneous glands was found.

As to the nature of the disease, it must be looked on as a congenital anomaly, a form of malformation in the widest sense of the word, which has affected more or less extensive parts of the nervous system and also expresses itself in symptoms on the part of other portions of the organism or even in the entire constitutional makeup. This conception is based on various grounds: (1) the fact that the disease or some of its most prominent features may be congenital or at least arise in early childhood; (2) that the disease often develops on a pronounced hereditary basis; (3) that the tumors show a primary multiplicity, which experience has shown to be a sign of congenital anomaly; (4) that the disease is not infrequently combined with congenital anomalies and malformations of various kinds. But it is often true that the congenital disposition remains latent for a long time and then, on account of various etiologic factors, calls forth tumors of skin and nerves. In what this congenital anomaly of the nervous system consists we know nothing, but we must assume that it is situated in and affects the connective tissue parts of the nerves. That the development of the tumors, as has been supposed, should be directly due to an influence exerted by the central nervous system is without foundation, and is, in itself, highly improbable, nor does the distribution and localization of the cutaneous tumors and pigmented areas support such a hypothesis. The pigment anomalies, as constituting an important and very frequent symptom, must be considered part of the whole clinical picture. Histologically the pigment in the skin was similar to that in all other accumulations of pigment, and I have not succeeded in establishing a connection between these pigment anomalies and pathologic conditions, tumors or other changes of the cor-

responding nerves. It appears reasonable at present, therefore, to look on the abnormal pigmentations as expressions of the same congenital disposition which has coincidentally caused the development of the abnormalities of the nervous system, but their exact connection is for the present entirely in the dark.



# FURTHER OBSERVATIONS ON THE RELATION OF IODIN TO THE STRUCTURE OF THE THYROID GLAND IN THE SHEEP, DOG, HOG AND OX \*

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## INTRODUCTION

In this report we have collected our observations on the relation of the iodine content to the structure of the thyroid to include sheep, ox and hog thyroids. It is thus only a continuation of the work previously reported<sup>1</sup> concerning dogs' thyroids. The methods used and the anatomic classifications adopted are the same as those fully described in the above-mentioned article and elsewhere.<sup>2</sup>

## COMPARISON OF THE IODINE CONTENTS OF SHEEP, DOG, HOG AND OX THYROIDES WITH THEIR RESPECTIVE ANATOMIC STRUCTURES

The following tables are compiled from iodine determinations made on the thyroids of 40 sheep, 67 dogs, 26 hogs and 37 oxen. As the basis of these tables we have used nine anatomic groups, viz.:

1. Normal glands.
2. Colloid glands (goiters).
3. Colloid-early glandular hyperplasia.
4. Normal-early glandular hyperplasia.
5. Early-glandular hyperplasia.
6. Early-moderate glandular hyperplasia.
7. Moderate glandular hyperplasia.
8. Moderate-marked glandular hyperplasia.
9. Marked glandular hyperplasia.

The normal and colloid groups are well defined, while the remaining seven groups are purely arbitrary divisions of the hyperplasias made for the purpose of facilitating analysis, since in reality one has to deal with a continuous gradation of hyperplastic changes occurring in either normal or colloid glands. In order to express this gradation, we have used the following terms: *normal-early glandular hyperplasia* to include

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\* From the Laboratories of Experimental Medicine and Pharmacology, Western Reserve University.

1. Marine (David) and Williams (W. W.): THE ARCHIVES INT. MED., 1908, i, 349.

2. Marine (David): The occurrence and physiological nature of glandular hyperplasia, etc. Johns Hopkins Hosp. Bull., 1907, xviii, 359.

those glands showing the very earliest hyperplastic changes occurring in normal glands; *colloid-early glandular hyperplasia* to include glands showing the earliest hyperplastic changes occurring in colloid glands, and the terms *early, moderate, marked, etc.*, to include the other gradations up to and including the most extensive glandular hyperplasias met with.

In placing these glands in these several anatomic groups, we have compared all the glands of the four animals, the one with the other, in order that the same standard of classification might obtain in all.

In each of the following tables we have listed for comparison the iodine contents of sheep, dog, hog and ox thyroids having the same anatomic structure.

TABLE 1.—NORMAL GLANDS \*

Animal.	No. Cases.	Iodin per gm. dried.			Iodin per gm. fresh.		
		E.	M.	A.	E.	M.	A.
Sheep .....	19	4.614	2.288	2.467	1.318	0.694	0.686
		1.247			0.318		
		4.722			1.064		
Dog .....	3		3.205	3.322		0.757	0.777
		1.990			0.512		
		4.153			1.456		
Hog .....	18		2.412	2.515		0.778	0.884
		1.538			0.425		
		4.768			1.592		
Ox .....	17		3.254	3.461		1.069	1.117
		2.730			0.892		

\* In each table E., M., A. are abbreviations for extreme, mean and average, respectively.

It will be seen that the upper extremes of iodine contents are fairly constant for all four animals, while the lower extremes show moderately wide variations, although the lowest of these lower extremes is always far in excess of the highest extremes of the succeeding group—normal-early glandular hyperplasias. This would indicate that there are considerable variations in the iodine contents within the group, even when no noteworthy anatomic changes are observed, although if individual comparisons of the iodine contents with the corresponding histologic preparations be made one can distinguish changes in the structure (too slight to warrant the introduction of a new group) corresponding to the variations in the iodine content; that is, glands with the highest iodine contents have a more flattened alveolar epithelium and *vice versa*, although all these glands appear in the table as normal.

The average iodine contents for the four animals show a surprising constancy and parallelism, viz.: 2.467 mg. for the sheep, 2.515 for the hog, 3.322 for the dog and 3.461 for the ox per gm. of dried thyroid.

The ox thyroids in our series have distinctly higher iodine contents than either the dog, sheep or hog. To know whether this is normally true would be of value in determining what relation exists between the normal iodine content and the normal weight of the thyroid, since oxen appear to have less thyroid per kilogram of body weight than do the other animals mentioned. From the experimental side it has been definitely shown that the amount of iodine in the thyroid does to a great extent control the size of the gland.

TABLE 2.—COLLOID GLANDS

Animal.	No. Cases.	Iodin per gm. dried.			Iodin per gm. fresh.		
		E.	M.	A.	E.	M.	A.
		3.691			1.027		
Sheep .....	3		3.529	2.996		0.974	0.818
		1.769			0.455		
		3.608			1.039		
Dog .....	8		1.816	1.985		0.406	0.459
		0.846			0.132		
		2.768			0.805		
Hog .....	2		.....	2.353		.....	0.681
		1.938			0.557		
Ox .....	0	.....	.....	.....	.....	.....	.....

Owing to the small number of cases included, it is not possible to speak very specifically. However, in all three animals in which colloids were observed the upper extremes of iodine content are fairly constant, while the lower extremes show moderate variations. This agrees with what was observed in the normal glands, and our explanation is the same. Another point worthy of note is that, while the iodine per gram of colloid gland is in general lower than that of normal glands, yet, as will be seen, they approach nearest to the normal iodine content so far as we have found and may be raised to an equal content with the normal glands.

TABLE 3.—COLLOID-EARLY GLANDULAR HYPERPLASIA

Animal.	No. Cases.	Iodin per gm. dried.			Iodin per gm. fresh.		
		E.	M.	A.	E.	M.	A.
		1.000			0.282		
Sheep .....	4		0.853	0.792		0.201	0.206
		0.461			0.138		
		1.443			0.302		
Dog .....	4		0.953	0.945		0.221	0.217
		0.431			0.125		
Hog .....	0	.....	.....	.....	.....	.....	.....
Ox .....	0	.....	.....	.....	.....	.....	.....

Table 3 and Table 4 deal with the most important anatomic and chemical changes concerned with the production of goiter, in that they represent the first deviation or change from the normal-colloid or quiescent glands. *Colloid-early glandular hyperplasias* differ from *normal-early glandular hyperplasias* in that the former are *secondary*<sup>3</sup> hyperplasias, while the latter are *primary*. It is to be regretted that more colloid-early glands were not obtainable (the probable reason for this will be pointed out later). The extremes show a fair constancy. In the sheep the highest extreme iodine content is below the lowest pure colloid extreme. In the case of the dog this is in general true, though there are exceptions which we are not able to explain. The existence of these exceptions suggests, however, that from the histology alone one is unable to say whether a given gland is undergoing further hyperplasia from a less marked hyperplasia or *vice versa*. The averages also are constant and in every instance show the great drop in the percentage of iodine from that of pure colloid glands. This drop is, as will be seen in Table 4, identical with that occurring between the normal and normal-early glandular hyperplasia. Between no other groups are there comparable drops. This means that in both colloid and normal glands there are wide variations in the amount of iodine present, but that there is a quite constant lower limit of the iodine content necessary to maintain normal gland or pure colloid gland structure, and that this lower limit for colloids is slightly in excess of 0.217 mg. per gram of fresh thyroid for dogs and 0.206 mg. per gram of fresh gland for sheep, corresponding to 0.792 mg. and 0.945 mg. per gram of dried gland, respectively.

TABLE 4.—NORMAL-EARLY GLANDULAR HYPERPLASIA

Animal.	No. Cases.	Iodine per gm. dried.			Iodine per gm. fresh.		
		E.	M.	A.	E.	M.	A.
Sheep .....	1	.....	.....	0.677	.....	.....	0.176
		1.296			0.318		
Dog .....	7	0.483	0.815	0.879	0.018	0.153	0.174
Hog .....	1	.....	.....	1.230	.....	.....	0.337
		2.676			0.726		
Ox .....	7	2.000	2.307	2.317	0.482	0.653	0.628

Table 4, together with Table 3, deals with the most important thyroid changes concerned in the production of goiter. It is seen that the highest extremes of iodine content are invariably below the lowest extreme

3. Secondary in the sense that this is the second time these glands have undergone active hyperplasia.

iodin contents of normal glands. This is even more evident with the means and averages. The table also shows that there is considerable difference between the average iodine content of sheep's thyroids and that of oxen thyroids, just as was seen to be true of the normal glands of these animals. It suggests, as was stated under Table 1, that oxen normally have more iodine and less thyroid per kilogram of body weight. In accordance with this, hyperplastic changes are manifest with an iodine content nearly four times that of the sheep's thyroids. But the most striking thing, just as in the colloid-early glands, is the great drop in iodine content from the normal, which must occur before hyperplastic changes are observed. The table shows that the lower limit of iodine necessary for the maintenance of normal structure is somewhat in excess of 0.176 mg. per gram of fresh gland for sheep, 0.174 for dogs, 0.337 for hogs and 0.628 for cattle, or 0.677, 0.879, 1.230, 2.317 mg. per gram of dried gland, respectively.

TABLE 5.—EARLY GLANDULAR HYPERPLASIA

Animal.	No. Cases.	Iodin per gm. dried.			Iodin per gm. fresh.		
		E.	M.	A.	E.	M.	A.
Sheep .....	0	.....	.....	.....	.....	.....	.....
		1.028			0.235		
Dog .....	9	0.243	0.654	0.625	0.063	0.113	0.139
		1.158			0.291		
Hog .....	2	1.046	.....	1.102	0.279	....	0.285
		2.186			0.615		
Ox .....	3	1.123	1.630	1.646	0.314	0.456	0.462

In the group of early glandular hyperplasia the iodine contents are still further lowered and the drop is practically the same in all four animals. The ox thyroids still show higher iodine contents than the other animals' glands for the same degree of thyroid hyperplasia as was also noted in the normal and normal-early glands.

TABLE 6.—EARLY-MODERATE GLANDULAR HYPERPLASIA

Animal.	No. Cases.	Iodin per gm. dried.			Iodin per gm. fresh.		
		E.	M.	A.	E.	M.	A.
Sheep .....	1	.....	.....	0.548	.....	.....	0.131
Dog .....	1	.....	.....	0.262	.....	.....	0.082
		0.846			0.241		
Hog .....	3	0.769	0.769	0.795	0.198	0.233	0.224
		1.030			0.252		
Ox .....	5	0.969	1.000	1.000	0.205	0.222	0.226

In the table of early-moderate glandular hyperplasia are collected those glands which histologically show a degree of epithelial proliferation (hyperplasia) too pronounced to be considered as early glandular hyperplasia and not sufficient to be classed as moderate glandular hyperplasia. As regards their iodine contents, the upper extremes are in every instance lower than the lower extremes of the preceding group (early glandular hyperplasia). So also the average iodine contents are about as much below those of the group of early glandular hyperplasias as the early glandular hyperplasias are below the group of normal-early glandular hyperplasias.

TABLE 7.—MODERATE GLANDULAR HYPERPLASIA

Animal.	No. Cases.	Iodin per gm. dried.			Iodin per gm. fresh.		
		E.	M.	A.	E.	M.	A.
Sheep .....	1	.....	.....	0.400	.....	.....	0.091
		0.854			0.136		
Dog .....	9	0.101	0.345	0.368	0.026	0.076	0.078
Hog .....	0	.....	.....	.....	.....	.....	.....
Ox .....	0	.....	.....	.....	.....	.....	.....

There being no glands from hogs or oxen and but one from the sheep series that histologically belonged to the group of moderate glandular hyperplasia, comparisons are impossible. The average iodine contents of the cases recorded are as usual below those of the preceding group.

TABLE 8.—MODERATE-MARKED GLANDULAR HYPERPLASIA

Animal.	No. Cases.	Iodin per gm. dried.			Iodin per gm. fresh.		
		E.	M.	A.	E.	M.	A.
Sheep .....	5	0.092	0.024	0.031	0.014	0.003	0.004
		0.000			0.000		
		0.660			0.109		
Dog .....	9	0.058	0.231	0.283	0.011	0.042	0.055
Hog .....	0	.....	.....	.....	.....	.....	.....
Ox .....	0	.....	.....	.....	.....	.....	.....

In the group of moderate-marked hyperplasia also there are but two animals represented. The extremes of iodine content in the dog thyroids are widely separated. As has already been pointed out, it is impossible to tell from the histology alone whether a given gland is undergoing further hyperplasia or is reverting to a lesser degree, in which latter event the iodine would be higher. Another factor must also be considered, that is, that dogs live under far less constant conditions than sheep and

oxen. It will be shown later that the more constant the conditions of life the more constant are the iodine contents. The averages show the same drop in the iodine contents proportional to the degree of increase of the hyperplasia.

TABLE 9.—MARKED GLANDULAR HYPERPLASIA

Animal.	No. Cases.	Iodin per gm. dried.			Iodin per gm. fresh.		
		E.	M.	A.	E.	M.	A.
Sheep .....	6	0.036			0.006		
		0.000	0.000	0.006	0.000	0.000	0.001
Dog .....	18	0.640			0.123		
		0.008	0.073	0.114	0.002	0.014	0.023
Hog .....	0	.....	.....	.....	.....	.....	.....
Ox .....	5	0.270			0.062		
		0.077	0.215	0.189	0.016	0.042	0.041

Table 9 includes those glands having the most marked degree of thyroid hyperplasia and in consequence the lowest iodine contents. The only glands in which no estimable amount of iodine was found were in sheep, although, histologically, the degree of hyperplasia was no greater than in other glands which showed traces of iodine. The average iodine contents are all lower than the averages of the preceding group. So also the extremes are lower except in dogs' thyroids, in which the same wide variations are noted as in Table 8. Our explanation is the same.

## SUMMARY AND DISCUSSION

Table 10, showing average iodine contents, has been introduced both as a summary and to emphasize the relation which exists between the iodine contents and the corresponding histologic structure.

TABLE 10.—AVERAGES

Anatomic Groups.	Sheep.		Dog.		Hog.		Ox.	
	Iodin per gm. Dried.	Fresh.	Iodin per gm. Dried.	Fresh.	Iodin per gm. Dried.	Fresh.	Iodin per gm. Dried.	Fresh.
Normal .....	2.467	0.686	3.322	0.777	2.515	0.884	3.461	1.117
Normal-early ....	0.677	0.176	0.879	0.174	1.230	0.337	2.317	0.628
Early .....	.....	.....	0.625	0.139	1.102	0.285	1.646	0.462
Early-moderate ..	0.548	0.131	0.262	0.082	0.795	0.224	1.000	0.226
Moderate .....	0.400	0.091	0.368	0.078	.....	.....	.....	.....
Moderate-marked.	0.031	0.004	0.283	0.055	.....	.....	.....	.....
Marked .....	0.006	0.001	0.114	0.023	.....	.....	0.189	0.041
Colloid .....	2.996	0.818	1.985	0.459	2.353	0.681	.....	.....
Colloid-early ....	0.792	0.206	0.945	0.217	.....	.....	.....	.....

Since colloid glands differ from normal glands essentially in that they have undergone active hyperplasia, two series (1), normal, and (2), colloid, must be recognized. Taking up the normal series, which is

practically complete in that it contains all the gradations of hyperplasia, it is seen that in all four species of animals the strictly normal glands have the highest iodine contents and those with marked glandular hyperplasia the lowest. The intervening groups show progressive decline, depending on the extent of the hyperplasia. The greatest drop in iodine content between any two successive groups occurs between the normal and the normal-early glandular hyperplasias, that is, those glands showing the earliest histologic deviation from normal. This great drop occurs with all four species and is similar in nature to the drop which occurs between the pure colloid glands and the colloid-early glandular hyperplasias. As has been said, this drop suggests that there is a minimum iodine content necessary for the maintenance of the normal or colloid state of the gland, and, since the amount of iodine present in normal or colloid glands is, as a rule, far in excess of this minimum, it is possible that this difference represents the reserve or factor of safety.

Certain details of this relation of iodine to the structure of the glands are more clearly shown in the full Tables 11, 12 and 13. Here it will be seen that by arranging the iodine contents in series from minimum to maximum, the glands are also arranged in series according to their histology, their colloid contents and their weights. In other words, the weights of the glands vary directly with the degree of hyperplasia and inversely with the percentage iodine content; the stainable colloid varies inversely with the degree of hyperplasia and directly with the iodine content, and the degree of hyperplasia varies inversely with the iodine contents (the normal and colloid series being, of course, considered separately).

It is also noticed that within any anatomic group there is considerable variation in the iodine contents. This is for the greater part due to the arbitrary anatomic groups, since the glands show histologic variations corresponding to the iodine variations, but not sufficient to warrant separate grouping. In other words, the arbitrary groups but imperfectly represent the gradations which the complete tables fully picture.

It may also be added that no special stress is laid on the actual figures of the iodine determinations, but only their relative importance as a series has been considered. Other observers with other methods may obtain different figures, but the relation between the iodine content and the gland structures, we believe, will always be found constant.

Passing now to the colloid series, it will be seen that only two groups of colloid glands have been observed: (1) pure colloids, (2) colloid-early glandular hyperplasia. This is noteworthy because in our human collection (to be reported), using the same anatomic classification and



TABLE 11.—PIGS' THYROIDS

Case No.	Age. Sex.	Condition.	Locality.	Weight of Gland.	Color.	Consistency.	Colloid.	Normal.	Colloid.	Normal-Early.	Colloid-Early.	Early.	Early-Moderate.	Moderate.	Moderate-Marked.	Marked.	Iodin per gm. Dried.	Iodin per gm. Fresh.
P. 2.	10 mos. M.*	Good ..	Iowa.....	?	Fleshy red .....	Moderately soft.	Reduced.	..	..	..	..	+	..	..	..	..	0.769	0.198
P. 24.	10 mos. M.	"	" .....	?	" " .....	Moderately soft.	"	..	..	..	..	+	..	..	..	..	0.769	0.233
P. 21.	10 mos. F.	"	" .....	?	" " .....	Moderately soft.	"	..	..	..	..	+	..	..	..	..	0.846	0.241
P. 17.	10 mos. M	"	" .....	?	Yellow-red, transluc..	Moderate....	Visible ..	..	..	..	..	+	..	..	..	..	1.046	0.279
P. 7.	10 mos. F.	"	" .....	?	" " "	" .....	"	..	..	..	..	+	..	..	..	..	1.158	0.291
P. 16.	9 mos. F.	"	" .....	?	Clear yellow-red .....	Firm .....	"	..	..	+	..	..	..	..	..	..	1.230	0.337
P. 6.	10 mos. M.	"	" .....	?	" " "	" .....	Normal..	+	..	..	..	..	..	..	..	..	1.538	0.425
P. 18.	10 mos M	"	" .....	?	" " "	" .....	"	..	+	..	..	..	..	..	..	..	1.538	0.553
P. 5.	10 mos. F.	"	" .....	j	" " "	" .....	"	..	+	..	..	..	..	..	..	..	1.938	0.523
P. 19.	11 mos. M.	"	" .....	?	" " "	" .....	"	..	..	+	..	..	..	..	..	..	1.938	0.557
P. 25.	9 mos. F.	"	" .....	?	" " "	" .....	"	..	..	+	..	..	..	..	..	..	1.938	0.596
P. 12.	10 mos. F.	"	" .....	?	" " "	" .....	"	..	..	+	..	..	..	..	..	..	1.938	0.599
P. 20.	10 mos. M.	"	" .....	?	" " "	" .....	"	..	+	..	..	..	..	..	..	..	1.938	0.603
P. 4.	10 mos. F.	"	" .....	?	" " "	" .....	"	..	+	..	..	..	..	..	..	..	1.984	0.774
P. 26.	10 mos. F.	"	" .....	?	" " "	" .....	"	..	+	..	..	..	..	..	..	..	1.997	0.601
P. 10.	10 mos. M.	"	" .....	?	" " "	" .....	"	..	+	..	..	..	..	..	..	..	2.307	0.783
P. 23.	8 mos. M.	"	" .....	?	" " "	" .....	"	..	+	..	..	..	..	..	..	..	2.517	0.587
P. 14.	8 mos. M.	"	" .....	?	" " "	" .....	"	..	+	..	..	..	..	..	..	..	2.615	1.071
P. 11.	8 mos. F.	"	" .....	?	" " "	" .....	"	..	+	..	..	..	..	..	..	..	2.768	0.905
P. 9.	8 mos. M.	"	" .....	?	" " "	" .....	"	..	+	..	..	..	..	..	..	..	2.768	0.940
P. 8.	2 yrs. F..	"	?	?	Pale yellow, transluc.	" .....	"	..	..	+	..	..	..	..	..	..	2.768	0.805
P. 1.	10 mos. M.	"	Iowa.....	?	Clear yellow-red .....	" .....	"	..	+	..	..	..	..	..	..	..	3.230	1.121
P. 15.	8 mos M.	"	" .....	j	" " "	" .....	"	..	+	..	..	..	..	..	..	..	3.691	1.220
P. 3.	10 mos. M.	"	" .....	?	" " "	" .....	"	..	+	..	..	..	..	..	..	..	3.691	1.456
P. 22.	10 mos. F.	"	" .....	?	" " "	" .....	"	..	+	..	..	..	..	..	..	..	3.728	1.140
P. 13.	8 mos. F.	"	" .....	?	" " "	" .....	"	..	+	..	..	..	..	..	..	..	4.154	1.298

\*Age estimated by butchers.

TABLE 12.—CATTLE THYROIDS

General.					Gross.				Microscopical.								Chemical.		
Case. No.	Age.	Sex.	Condition.	Locality.	Weight of Glands in gms.	Color.	Consistency.	Colloid.	Normal.	Colloid.	Normal-Early.	Colloid-Early.	Early.	Early-Moderate.	Moderate.	Moderate-Marked.	Marked.	Iodin, per gm., Dried.	Iodin, per gm., Fresh.
C. 34.	Young steer.*		Good ..	Northern Ohio.	41	Opaque, pale brown.	Soft. ....	Absent ..	..	..	..	..	..	..	..	..	+	0.077	0.016
C. 36.	"	"	"	Northern Ohio.	53	Very pale brown....	" .....	" ..	..	..	..	..	..	..	..	..	+	0.154	0.031
C. 29.	Calf, female.		Poor ..	Michigan..	370	" " " ....	" .....	" ..	..	..	..	..	..	..	..	..	+	0.215	0.042
C. 30.	Young steer.		Good ..	Northern Ohio.	39	" " " ....	" .....	" ..	..	..	..	..	..	..	..	..	+	0.231	0.052
C. 35.	"	"	"	Northern Ohio.	13	Dark brown-red....	Moderate..	Visible..	..	..	..	..	..	..	..	..	+	0.270	0.062
C. 40.	"	"	"	Northern Ohio.	27	Brown red.....	" .....	" ..	..	..	..	..	..	+	..	..	..	0.969	0.205
C. 33.	"	"	"	Northern Ohio.	17	Dark brown-red....	" .....	" ..	..	..	..	..	..	+	..	..	..	0.969	0.205
C. 31.	"	"	"	Northern Ohio.	17	" " " ....	" .....	" ..	..	..	..	..	..	+	..	..	..	1.030	0.222
C. 37.	"	"	"	Northern Ohio.	16	Translucent, brown-red.	" .....	" ..	..	..	..	..	..	+	..	..	..	1.000	0.248
C. 38.	"	"	"	Northern Ohio.	19	Pale brown, translucent.	Firm .....	" ..	..	..	..	..	..	+	..	..	..	1.030	0.252
C. 39.	"	"	"	Northern Ohio.	16	Pale brown, translucent.	" .....	Normal..	..	..	..	..	+	..	..	..	..	1.123	0.314
C. 32.	"	"	"	Northern Ohio.	13	Brown red, translucent.	" .....	" ..	..	..	..	..	+	..	..	..	..	1.630	0.456
C. 65.	"	"	"	Northern Ohio.	12	Brown red, translucent.	" .....	" ..	..	..	+	..	..	..	..	..	..	2.153	0.482
C. 46.	"	"	"	Texas.....	12	Dark brown-red, translucent.	" .....	" ..	..	..	+	..	..	..	..	..	..	2.000	0.585
C. 51.	"	"	"	" .....	13	Pale brown-red, translucent.	" .....	" ..	..	..	..	..	+	..	..	..	..	2.186	0.615
C. 45.	"	"	"	" .....	13	Very pale yellow brown, translucent.	" .....	" ..	..	..	+	..	..	..	..	..	..	2.076	0.617
C. 48.	"	"	"	" .....	12	Pale yellow brown, translucent.	" .....	" ..	..	..	+	..	..	..	..	..	..	2.307	0.653
C. 64.	"	"	"	Northern Ohio.	13	Pale yellow brown, translucent.	" .....	" ..	..	..	+	..	..	..	..	..	..	2.615	0.664
C. 41.	Young bull..		"	Texas†.....	11.5	Pale yellow brown, translucent.	" .....	" ..	..	..	+	..	..	..	..	..	..	2.676	0.666
C. 42.	Young steer.		"	" .....	12	Pale yellow brown, translucent.	" .....	" ..	..	..	+	..	..	..	..	..	..	2.384	0.726
C. 47.	"	"	"	" .....	11	Yellow-brown, translucent.	" .....	" ..	+	..	..	..	..	..	..	..	..	2.730	0.892
C. 44.	"	"	"	" .....	15	Pale brown, translucent.	" .....	" ..	+	..	..	..	..	..	..	..	..	2.922	0.901
C. 43.	"	"	"	" .....	11	Pale brown, translucent.	" .....	" ..	+	..	..	..	..	..	..	..	..	2.937	0.952
C. 49.	"	"	"	" .....	11	Pale brown, translucent.	" .....	" ..	+	..	..	..	..	..	..	..	..	3.107	0.988
C. 52.	"	"	"	" .....	12	Brown red, translucent.	" .....	" ..	+	..	..	..	..	..	..	..	..	3.091	0.992
C. 57.	"	"	"	" .....	12	Pale yellow, translucent.	" .....	" ..	+	..	..	..	..	..	..	..	..	3.254	1.020
C. 56.	"	"	"	" .....	11	Pale yellow, translucent.	" .....	" ..	+	..	..	..	..	..	..	..	..	3.537	1.059
C. 63.	"	"	"	" .....	11	Pale yellow, translucent.	" .....	" ..	+	..	..	..	..	..	..	..	..	3.230	1.040
C. 55.	"	"	"	" .....	12	Pale yellow, translucent.	" .....	" ..	+	..	..	..	..	..	..	..	..	3.230	1.069
C. 50.	"	"	"	" .....	14	Pale yellow, translucent.	" .....	" ..	+	..	..	..	..	..	..	..	..	3.384	1.133
C. 62.	"	"	"	" .....	12	Pale yellow, translucent.	" .....	" ..	+	..	..	..	..	..	..	..	..	3.630	1.152
C. 61.	"	"	"	" .....	12	Pale yellow, translucent.	" .....	" ..	+	..	..	..	..	..	..	..	..	3.630	1.161
C. 60.	"	"	"	" .....	11	Pale yellow, translucent.	" .....	" ..	+	..	..	..	..	..	..	..	..	3.230	1.208
C. 58.	"	"	"	" .....	12	Pale yellow, translucent.	" .....	" ..	+	..	..	..	..	..	..	..	..	3.999	1.215
C. 53.	"	"	"	" .....	13	Pale yellow, translucent.	" .....	" ..	+	..	..	..	..	..	..	..	..	3.999	1.292
C. 54.	"	"	"	" .....	11	Pale yellow, translucent.	" .....	" ..	+	..	..	..	..	..	..	..	..	4.153	1.347
C. 59.	"	"	"	" .....	11	Pale yellow, translucent.	" .....	" ..	+	..	..	..	..	..	..	..	..	4.768	1.592

\*i.e. 3 to 5 yrs. as estimated by cattlemen.

†General term among cattlemen, meaning any part of Great Plains.

TABLE 13.—SHEEP THYROIDS

General.				Gross.				Microscopical.								Chemical.		
Case No.	Ago. Sex.	Condition.	Locality.	Weight in gms.	Color.	Consistency.	Colloid.	Normal.	Colloid.	Normal-Early.	Colloid-Early.	Early.	Early-Moderate.	Moderate.	Moderate-Marked.	Marked.	Iodin, per gm., Dried.	Iodin, per gm., Fresh.
S. 33.	F 8 mos...	Good...	Seville, Ohio.	95.0	Gray red, translucent.	Soft. ....	Visible...	..	..	..	..	..	..	..	..	+	0.000	0.000
S. 37.	M. 10 mos .	" ..	Seville, Ohio.	115.0	Gray red, opaque...	" .....	None ....	..	..	..	..	..	..	..	..	+	0.000	0.000
S. 39.	M. 9 mos...	" ..	Seville, Ohio.	85.0	" " " "	" .....	" .....	..	..	..	..	..	..	..	..	+	0.000	0.000
S. 45.	M. 8 mos...	" ..	Seville, Ohio.	55.0	" " " "	" .....	" .....	..	..	..	..	..	..	..	..	+	0.000	0.000
S. 20.	? 8 mos...	" ..	?	110.0	" " " "	" .....	" .....	..	..	..	..	..	..	..	..	+	0.000	0.000
S. 36.	M. 9 mos...	" ..	Seville, Ohio.	120.0	Gray, translucent...	" .....	Visible...	..	..	..	..	..	..	..	..	+	0.000	0.000
S. 38.	M. 10 mos..	" ..	Seville, Ohio.	130.0	" " " "	" .....	" .....	..	..	..	..	..	..	..	..	+	0.024	0.003
S. 31.	F. 9 mos...	" ..	Seville, Ohio.	98.0	" " " "	" .....	" .....	..	..	..	..	..	..	..	..	+	0.040	0.005
S. 35.	F. 9 mos...	" ..	Seville, Ohio.	110.0	" " " "	" .....	" .....	..	..	..	..	..	..	..	..	+	0.036	0.006
S. 59.	? 1 yr....	" ..	?	6.0	Opaque, red, granular.	" .....	None....	..	..	..	..	..	..	..	..	+	0.092	0.014
S. 21.	M. 1 yr....	" ..	?	61.0	Opaque, red, granular.	" .....	" .....	..	..	..	..	..	..	..	..	+	0.400	0.091
S. 49.	F. 8 mos...	" ..	?	48.0	Opaque, red, granular.	" .....	" .....	..	..	..	..	..	..	..	..	+	0.518	0.131
S. 47.	M. 9 mos...	" ..	?	6.0	Red-gray, translucent.	Moderate....	" .....	..	..	..	..	..	..	..	..	+	0.461	0.138
S. 32.	F. 4 yrs....	Fair... ?	?	370.0	Red-yellow, translucent.	Firm .....	Normal..	..	..	..	+	..	..	..	..	..	0.677	0.176
S. 43.	F. 5 yrs....	" ... ?	?	15.0	Red-yellow, translucent.	" .....	Visible...	..	..	..	+	..	..	..	..	..	0.923	0.201
S. 51.	M. 9 mos...	Good... ?	?	18.0	Red-yellow, translucent.	" .....	" .....	..	..	..	..	+	..	..	..	..	0.784	0.202
S. 50.	M. 9 mos...	" .. ?	?	16.0	Red-yellow, translucent.	" .....	" .....	..	..	..	..	..	+	..	..	..	1.000	0.282
S. 46.	F. 5 yrs....	Fair... ?	?	25.0	Clear yellow, translucent.	" .....	Normal..	..	..	..	..	+	..	..	..	..	1.260	0.308
S. 52.	? 1 yr....	Good... ?	?	5.9	Clear yellow, translucent.	" .....	" .....	..	..	..	..	..	..	..	..	..	1.247	0.313
S. 53.	? 1 yr....	" .. ?	?	6.7	Clear yellow, translucent.	" .....	" .....	..	..	..	..	..	..	..	..	..	1.425	0.365
S. 55.	? 1 yr....	" .. ?	?	6.5	Clear yellow, translucent.	" .....	" .....	..	..	..	..	..	..	..	..	..	1.602	0.405
S. 48.	F. 9 mos...	Fair... ?	?	5.9	Clear yellow, translucent.	" .....	" .....	..	..	..	..	..	..	..	..	..	1.615	0.430
S. 63.	F. 3 yrs....	Good... ?	?	8.0	Clear yellow, translucent.	" .....	" .....	..	..	..	..	..	..	..	..	..	1.769	0.455
S. 60a	M. 2 yrs....	" .. ?	?	58.0	Clear yellow, translucent.	" .....	" .....	..	..	..	..	..	..	..	..	..	1.812	0.468
S. 58.	? 1 yr....	" .. ?	?	4.5	Clear yellow, translucent.	" .....	" .....	..	..	..	..	..	..	..	..	..	2.153	0.564
S. 60.	F. 3 yrs....	Fair... Northern Ohio.	Northern Ohio.	8.0	Clear yellow, translucent.	" .....	" .....	..	..	..	..	..	..	..	..	..	2.288	0.582
S. 61.	F. 3 yrs....	" .. Northern Ohio.	Northern Ohio.	8.5	Clear yellow, translucent.	" .....	" .....	..	..	..	..	..	..	..	..	..	2.153	0.608
S. 62.	F. 4 yrs....	" .. Northern Ohio.	Northern Ohio.	8.0	Clear yellow, translucent.	" .....	" .....	..	..	..	..	..	..	..	..	..	2.392	0.694
S. 65.	F. 4 yrs....	" .. Northern Ohio.	Northern Ohio.	8.5	Clear yellow, translucent.	" .....	" .....	..	..	..	..	..	..	..	..	..	2.250	0.727
S. 44.	F. 4 yrs....	" .. ?	?	6.0	Clear yellow, translucent.	" .....	" .....	..	..	..	..	..	..	..	..	..	2.644	0.735
S. 67.	? 1 yr....	" .. ?	?	7.5	Clear yellow, translucent.	" .....	" .....	..	..	..	..	..	..	..	..	..	3.292	0.823
S. 57.	? 1 yr....	" .. ?	?	5.4	Clear yellow, translucent.	" .....	" .....	..	..	..	..	..	..	..	..	..	3.054	0.861
S. 70.	F. 4 yrs....	" .. Northern Ohio.	Northern Ohio.	7.0	Clear yellow, translucent.	" .....	" .....	..	..	..	..	..	..	..	..	..	3.058	0.872
S. 69.	F. 3 yrs....	" .. Northern Ohio.	Northern Ohio.	8.0	Clear yellow, translucent.	" .....	" .....	..	..	..	..	..	..	..	..	..	3.150	0.872
S. 66.	F. 3 yrs....	" .. Northern Ohio.	Northern Ohio.	7.5	Clear yellow, translucent.	" .....	" .....	..	..	..	..	..	..	..	..	..	2.500	0.890
S. 54.	? 1 yr....	Good... ?	?	6.55	Clear yellow, translucent.	" .....	" .....	..	..	..	..	..	..	..	..	..	3.691	0.974
S. 64.	? 1 yr....	" .. Northern Ohio.	Northern Ohio.	8.0	Clear yellow, translucent.	" .....	" .....	..	..	..	..	..	..	..	..	..	3.529	1.027
S. 19.	M. 2 yrs....	Excellent.	?	52.0	Clear yellow, translucent.	" .....	" .....	..	..	..	..	..	..	..	..	..	4.368	1.200
S. 56.	M. 1 yr....	Good... ?	?	6.4	Clear yellow, translucent.	" .....	" .....	..	..	..	..	..	..	..	..	..	4.614	1.318
S. 68.	M. 10 mos..	" ..	Northern Ohio.	7.5	Clear yellow, translucent.	" .....	" .....	..	..	..	..	..	..	..	..	..		

methods, the colloid series will contain sufficient gradations of the hyperplasias to parallel the normal series throughout and will be discussed with equal emphasis.

These two groups of colloid glands suffice, however, to illustrate, first, the fact that pure colloid glands of the different animals have iodine contents very closely approaching those of normal glands, and, second, that colloid-early glandular hyperplasias have iodine contents similarly close to those with normal-early glandular hyperplasias. We believe that if all the conditions (diet, etc.) could be strictly controlled the iodine content of colloid glands would absolutely parallel those of normal glands and that a like parallelism would be seen throughout the gradations of hyperplasia of both the normal and colloid series.

The probable reasons why we rarely obtain colloid glands in sheep, cattle and hogs are (1) that they are killed at an age when the natural occurrence of colloid glands is rare, and (2) that the conditions of life (as regards habits, food and locality) are more constant than obtain for man or dogs.

So striking a uniformity in the anatomic changes for widely different animals can not be without significance. It suggests that the etiologic factor or factors in the production of thyroid hyperplasia (goiter) are probably the same in all these animals. The constant relation between structure and iodine content suggests that iodine is a common factor in all these animals.

It seems fair to infer from this comparative study of anatomic structure and iodine content that iodine is a very important factor, acting in the same direction and manner in all classes of animals in which hyperplasias (goiterous changes) are observed, and that, therefore, for a general study of goiter, any of the animals mentioned may be used as a basis, and the results be applicable to man.

NOTE.—In conclusion we wish to thank Professors Torald Sollmann and G. N. Stewart for their careful criticisms and suggestions.

## EXPERIMENTAL MYOCARDITIS \*

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PHILADELPHIA

During the course of our experiments regarding the influence of various substances and conditions on the production of edema it was deemed advisable to use some animals in which there was a heart lesion in order to note the effect of chronic myocarditic lesions on the production of ascites, intestinal fluid and urine.

Experimental lesions of the myocardium have been produced and described by a number of observers. Ribbert,<sup>1</sup> by injecting intravenously cultures of *Staphylococcus pyogenes aureus* into rabbits, was able to produce both endocardial and myocardial lesions, the latter consisting of a central necrotic area surrounded by a wall of polynuclear leucocytes; none of the animals treated in this manner survived the injection for any great length of time. Zwasehkewitsch<sup>2</sup> found that the hearts of animals exposed to high temperatures for a considerable period of time showed a cloudy swelling of the muscle fibers; Litten,<sup>3</sup> Naunyn,<sup>4</sup> Nasaroff,<sup>5</sup> Werhovsky<sup>6</sup> and Welch<sup>7</sup> found that animals exposed to a temperature of about 40 degrees for several days showed not cloudy swelling but fatty degeneration of the heart muscle.

Many investigators have studied the changes produced in the heart by the diphtheria bacillus. Babes<sup>8</sup> has shown that the effects produced by the injection of diphtheria toxin are the same as those produced by the inoculation of the organisms themselves. Charrin,<sup>9</sup> Welch and Flexner,<sup>10</sup> Mollard and Regaud<sup>11</sup> and Flexner<sup>12</sup> have described the cardiac lesions caused by this toxin and found, as the principal condi-

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\*From the Laboratory of Experimental Pathology, University of Pennsylvania.

1. Ribbert: *Fortschr. d. Med.*, 1886, iv, 1.

2. Zwasehkewitsch: *Dissertation*, St. Petersburg, 1870.

3. Litten: *Virchow's Arch. f. path. Anat.*, 1887, lxx, 10.

4. Naunyn: *Arch. f. exper. Path.*, 1884, xviii, 49.

5. Nasaroff: *Virchow's Arch. f. path. Anat.*, 1882, xe, 482.

6. Werhovsky: *Beitr. z. path. Anat. u. z. allg. Path.* (Ziegler's), 1895, xviii, 72.

7. Welch: *Med. News*, 1888, lii, 365.

8. Babes: *Virchow's Arch. f. path. Anat.*, 1896, exix, 460.

9. Charrin: *Semaine m  d.*, 1890, x, 285.

10. Welch and Flexner: *Johns Hopkins Hosp. Bull.*, 1891, ii, 107. Welch and Flexner: *Johns Hopkins Hosp. Bull.*, 1892, iii, 17.

11. Mollard and Regaud: *Ann. de l'Inst. Past.*, 1892, xi, 97.

12. Flexner: *Johns Hopkins Hosp. Rep.*, 1897, vi, 259.

tions, fatty metamorphosis of the muscle fibers, swelling and elongation of the nuclei, atrophy of the fibers with an increase of the sarcoplasm of the fibers (*atrophie hyperplasmique*—Mollard and Regaud), interstitial edema and infiltration of leucocytes. In their later communication Mollard and Regaud<sup>13</sup> find increased connective tissue replacing the lost muscle substance; this does not appear, however, until several months after the injection of the toxin. Tallquist,<sup>14</sup> by the injection of cultures of streptococci directly into the heart muscle, produced suppurative areas and degeneration of the muscle fibers. Baumgarten<sup>15</sup> produced heart lesions in dogs by ligation of branches of the coronary vessels and found under such conditions degeneration of the muscular substance and subsequent replacement by connective tissue.

Since within the past five years adrenalin has been so widely used in the production of arterial lesions in rabbits, a number of observations have been made as regards the effect of this substance in producing heart lesions. These lesions have been variously described as hypertrophy, interstitial myocarditis or necrosis of the myocardium.

K. Ziegler,<sup>16</sup> in some experiments regarding the effect of repeated injections of small doses of adrenalin in producing arterial lesions, found cardiac lesions in a large percentage of his animals. As early as six days after the first injection, the animal having received in all six injections, he found hemorrhage and edema of parts of the myocardium, round-cell infiltration at various places and vacuoles in the muscle fibers. After a large number of injections, and ten days after the first injection, he noted the presence of increased connective tissue which takes its origin from the blood vessels and the endocardium. At a later period he speaks of the occurrence of anemic infarcts and areas of induration, and seven months after the first injection Ziegler finds a hypertrophic condition of the heart.

Pearce<sup>17</sup> examined a group of animals which received from seven to fifteen injections and which were killed at various periods after the first injection; he also reports on another group of animals which died immediately after the injection and which had received from one to five injections. He did not report any chronic myocardial lesions which followed one injection. In animals which died immediately after one injection

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13. Mollard and Regaud: *Compt. rend Soc. biol.*, 1897, p. 674.

14. Tallquist: *Beitr. z. path. Anat. u. z. allg. Path.* (Ziegler's), 1899, xxv, 159.

15. Baumgarten: *Am. Jour. Physiol.*, 1899, ii, 243.

16. Ziegler (K.): *Beitr. z. path. Anat. u. z. allg. Path.* (Ziegler's), 1905, xxxviii, 229.

17. Pearce: *Jour. Exper. Med.*, 1906, viii, 400.

of adrenalin he noted edema separating the muscle fibers, which showed irregular swellings and a lessened clearness of the striations. In all the other animals in which he described myocardial lesions these appeared after a series of injections and were examined at various periods after the first injection. There could be seen increase of the connective tissue, swollen nuclei, the appearance of a non-staining zone about the nuclei, and loss of striations. In the late stages the fibers were swollen, often vacuolated, and appeared to have undergone a hyaline transformation. We find that on the whole Pearce's results confirm the findings of Ziegler; both report early degenerative changes in the muscle fibers, and these are followed by an increase of connective tissue.

Gröber<sup>18</sup> has described a cardiac hypertrophy which was proportionate to the number of injections of adrenalin, and the occurrence of vascular lesions, and he believes that the hypertrophy of the heart is due to the vascular lesions.

These publications regarding the production of myocarditic changes by the repeated injections of adrenalin do not give sufficient data, or the number of the experiments is so small that no conclusion can be drawn as to the frequency of their occurrence. It has, furthermore, been impossible to give an accurate description of the sequence of the changes in so far as the various specimens examined differed, not only as regards the time which had passed since the first injection, but also in regard to the number of injections and the quantity of adrenalin used. There are, therefore, a number of variable factors present in each rabbit which do not permit of an accurate determination of the importance of the time factor. Furthermore, if we wish to use a large number of animals with myocardial lesions for experimental purposes, the treatment of animals by repeated injections of adrenalin is too tedious a process.

In the course of some work on edema of the lungs, the results of which will be published elsewhere, we noted that in some animals which had been injected with adrenalin and spartein sulphate there appeared after a short period of time a lesion of the left ventricle. We then conducted further experiments and found such lesions to occur quite constantly.

If we injected a rabbit intravenously with either spartein sulphate or sodium caffein benzoate, and two or three minutes later with 0.2 c.c. of a 1 to 1000 solution of adrenalin, after a period of ten to fourteen days this lesion of the left ventricle was noted. The amount of spartein

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18. Gröber: *Deutsch. med. Wchnschr.*, 1907, xxxiii, 744.

sulphate<sup>19</sup> which was used was 0.012 gm. per kilogram; of sodium caffeine benzoate, 0.025 gram per kilogram; the time interval between the injection of the spartein or caffeine and the adrenalin was not of vital importance, except that shortening the interval was likely in a large percentage of the animals to cause death; on the other hand, more than five minutes were never allowed to elapse between the injections.

We thus had a very simple method for producing the desired lesion and one which did not call for a long period of waiting. Of 82 rabbits which were injected in the above manner, 49 (60 per cent.) showed when examined macroscopically, a lesion of the left ventricle after periods varying from four days to six weeks after the injection. On microscopic examination, however, it was found that several hearts which had been set down as normal when examined macroscopically, really showed a more or less marked change. The occurrence of this lesion is, therefore, more frequent than would appear from the figures above, which refer only to those lesions seen by the naked eye.

#### MACROSCOPIC APPEARANCE

The lesion was in the left ventricle and with but one exception situated close to the base, at times running up to the auriculo-ventricular groove. Most frequently it was on the posterior surface of the heart wall toward the posterior interventricular sulcus. In size the lesion varied, at times being confined to the upper and posterior quarter of the left ventricle, at times involving all of the left ventricle except a small part of the apex. In one case the lesion involved only the tip of the apex, but this was the only case in which the apex was involved in the lesion. At times the changed area could not be noted on the exterior of the heart, but when the left ventricle was cut, on cross-section a small changed area could be noted in the center of the muscular wall. The papillary muscles were also frequently involved in the lesion. With the lapse of time the lesion does not become more extensive to the naked eye and some part of the wall of the ventricle always appears unchanged.

The appearance of the diseased area was distinctly contrasted with the normal red-brown of the heart muscle; the area was pale and of a yellow-brown color, which shaded off into the surrounding normal tissue. On palpation of the heart muscle there was a distinct sensation of stiffen-

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19. When using spartein sulphate we worked with two preparations, Merck's and Boehringer's, and we found that the latter was better adapted for the work, since it was far less irregular in its action and less lethal in its effect. In injecting animals weighing 2 kg. or more, it was found advisable to reduce the dose of spartein slightly.



ing and loss of pliability of the wall of the ventricle. On cutting through the area there was increased resistance. Almost invariably the thickness of the wall was increased, in some cases slightly, in others markedly. Such gross changes were noted as early as four days after the injection of adrenalin and spartein or caffeine, but were best seen from ten days onward. In one case as early as two days after the injection we were able to note a slight macroscopic change in the heart.

In two cases, one of an animal which died while being operated on under ether anesthesia, the other being killed by severing the spinal cord, the hearts were found unduly dilated. This dilatation was especially marked in the right ventricle, which in one case overlapped and almost hid the left ventricle; the auricles were also dilated so that when the thorax was opened the apex of the heart was thrown forward and upward.

#### MICROSCOPIC APPEARANCES

The microscopic changes were followed from a very early period, seven minutes after the injection, to a period six weeks after the injection.

The hearts of several rabbits which died but a few minutes after the injection were examined especially with the idea of discovering if there was any evidence of rupture or hemorrhage at the usual site of the lesion, but no such appearance could be noted; the only change seen was occasionally some separation of the muscle fibers suggesting interstitial edema.

After twenty-four hours we sometimes found separation of the individual fibers, perhaps due to edema between the fibers, a slight increase in the size of the muscle fibers, and at times around the nucleus the appearance of a clear area which did not take the stain.

Of two animals which were killed two days after injection, one showed a slight paling of the wall of the left ventricle at the place where the lesion was usually noted. In this heart the muscle fibers were torn apart and swollen, measuring on an average 13.6 micromillimeters as compared with the measurement of 7 to 10 micromillimeters for the muscle fibers of normal hearts; the cross striations were now slightly faded. The nuclei were larger, averaging  $14.5 \times 4.2$  micromillimeters as compared with  $10 \times 3.5$  micromillimeters in normal hearts, and the non-staining areas about the nuclei were frequently seen to be increased in size. Between the muscle fibers was seen an increased number of connective tissue cells. In the other heart, which showed no gross lesion, slight microscopic changes were seen, such as separation of the individual muscle fibers, increase of the non-staining area about the muscle nuclei and also areas where the connective tissue cells were increased.

Four days after the injection the changes had become quite marked and the edema between the muscle fibers was plainly visible. In some areas the fibers appeared to have been dissolved, although the presence of some nuclei of the muscle fibers was noted; these were surrounded by a thin ring of muscle substance. This dissolution had left the network of connective tissue uninjured and the connective tissue cells were increased in and about these areas. At other places the muscle fibers were increased in size and at times we noted vacuoles in them. The occurrence of double nuclei lying either in close contact or somewhat separated by sarcoplasm was somewhat more frequent than normal. At some places the muscle nuclei were beginning to disappear, taking the stain very faintly; at other places karyolysis of the nuclei had taken place. The degenerative changes were more marked in this specimen than in any of the later ones until a period of several weeks had elapsed after the injection.

At six days the increase of connective tissue had become quite apparent, most marked in the papillary muscles and near the endocardium. There was also an increase of the connective tissue around the vessels. The muscle fibers were more noticeably increased in size and were separated by interstitial edema. The striations were not so clear as normal, and we saw occasionally a granular appearance which seemed to be due to the breaking up of the fibrils. Double nuclei were seen quite frequently and occasionally we noted small areas of dissolution of the fibers. But few vacuoles were seen.

At nine days the changes had progressed and we saw clumps of young connective tissue cells between the fibers and about the blood vessels, in the papillary muscles the increase of connective tissue being quite marked and short strands of connective tissue were noted growing in from the endocardium. The muscle fibers were increased in size, showing the striation less clearly than normally but in places showing a marked longitudinal striation. Toward the endocardium where the fibers were surrounded by connective tissue there was quite a little vacuolization. The nuclei did not show much change; the occasional paleness and the increased occurrence of double nuclei were about the only noteworthy appearances.

In the specimens examined for the period between twelve and twenty-one days after the injection the changes as found in the different specimens varied but little, and they may be described in a general manner. The increase of connective tissue was diffuse, well marked about the blood vessels and near the endocardium and pericardium, but also seen between the muscle fibers. The pericardium was thickened and showed

an increase in connective tissue cells. The separation of the connective tissue fibers between the muscle elements, probably due to an edematous condition of the connective tissue, was quite marked. Nowhere were collections of polynuclear leucocytes or of small mononuclear cells to be seen. In some sections could be seen small areas where the muscle fibers were more or less dissolved, and throughout the fibrillar connective tissue network which was left behind were seen scattered the nuclei of the muscle fibers with a pale ring of muscle substance about them. The muscle fibers were increased in breadth and might measure as much as 16 or 18 micromillimeters. The cross striations were not so clear as normally but the longitudinal striations became more marked as the fibers increased in size. The appearance of vacuoles had become more frequent, but could by no means be said to be common; the vacuoles might be large or small: there might be several in one cell or one large one might occupy the center of a cell and produce the appearance of a ring cell. Vacuolization occurred usually where the muscle fibers were enclosed by new-formed connective tissue, but it also appeared in some areas independent of the connective tissue proliferation. Even more rarely there could be noted a granular appearance of the muscle which was associated with a breaking down of the muscle substance. Frequently there was seen an increase in the size of the sarcoplasm spindle which had attained about three times its usual size. Not all muscle fibers were hypertrophied, however; occasionally there were noted fibers distinctly atrophic with an increase in the perinuclear pigment. The nuclei were larger than normal and the number of double nuclei might be markedly increased; at times as many as fifty-six such pairs might be seen in twenty microscopic fields, while in the normal heart there is seen only one pair in every second field (eleven pairs in twenty-two fields). We also noticed here not infrequently the presence of two nucleoli in one muscle nucleus which perhaps represented the first stages in the amitotic division of the muscle nucleus.

When a period of six weeks had intervened since the injection the changes were found to be far more marked in the one heart which we have so far examined microscopically. The connective tissue had now increased quite markedly and separated the individual muscle fibers; the increase was present in the papillary muscles as well as in the wall of the ventricle. It was not limited to the endocardial, pericardial or vascular connective tissue, but was found throughout the myocardium, all the pre-existing connective tissue seeming to have taken part in the increase. The muscle fibers were quite generally increased in size and were paler than normally, vacuoles in the cells did not destroy the cross

striations, although these striations were not so clear as in the normal heart. Longitudinal striation was marked and gave the appearance of a separation of the individual fibrils. Double nuclei were quite frequent in the muscle cells. There were many areas of dissolution of the muscle fibers in which, as usually, the connective tissue fiber network and atrophied muscle fibers were left behind.

Eight hearts which macroscopically appeared normal after the injections were examined microscopically, and seven of these showed the presence of some change corresponding to the condition just described and at times quite as marked. In such hearts which macroscopically appear normal there was generally found connective tissue overgrowth, not very pronounced increase in the size of the fibers, and some separation of the muscle fibers (interstitial edema?).

The principal changes which are produced by the injection of adrenalin and spartein, etc., are, therefore, the following: We find very early increase in the size of the muscle fibers and increase in the number of muscle nuclei, the cross striation is somewhat less clear than in the normal heart; at a very early period we also find increase in the connective tissue fibers and isolated areas in which degenerative processes in the muscle fibers can be seen, such degenerative processes becoming more marked at somewhat later stages.

The interstitial change begins soon after the injection, as early as two days, and becomes steadily more marked; in the early periods it is only noticeable about the blood vessels, endocardium and pericardium, but later it becomes diffuse and all the connective tissue elements seem to take part in the proliferation. In the parenchyma the principal change is the increase in size of the fibers which makes its appearance early and also becomes progressively more marked. There appears an increase in the clear area about the nucleus and the cross striations become faint, while the longitudinal striations become more marked. Quite late there appear vacuoles in the muscle fibers; there also are seen areas of dissolution and atrophy of the muscle fibers. The increase of the number of double nuclei is found at six to nine days and reaches its maximum at fourteen to eighteen days.

We find, therefore, in these lesions a combination of: first, hypertrophic changes in the muscle fibers and nuclei; second, increase in connective tissue; third, degenerative changes in the muscle fibers. If we compare these findings with the description of the changes in hypertrophic human hearts as described by Krehl, Albrecht and others we are struck by the similarity of the changes found in the two sets of conditions, namely: in our experimentally produced myocarditic lesions and

in cases of hypertrophy of human hearts which originated under natural conditions. In all the latter we find the same combination of hypertrophy of muscle fibers, increase of connective tissue and degeneration of muscle fibers.

Krehl,<sup>20</sup> examining human hearts which showed either idiopathic hypertrophy or hypertrophy secondary to valvular lesions, has shown by careful and painstaking study that various pathologic conditions may be noted. He has noted a thickening and overgrowth of the pericardium, changes in the blood vessels, such as thickening, arteritis obliterans, or a round-cell infiltration of the muscular coat. Between the muscle fibers there is a round-cell infiltration and in places induration and cirrhosis, which has caught and destroyed the muscle fibers, leaving only the muscle nuclei. Vacuoles were seen as well as an increase of pigment at the poles of the nuclei; fatty changes were seldom noted. The muscle fibers were increased in size. Krehl considered these conditions which he found scattered in small areas throughout the heart as due to some injurious substance, probably the same as that which produced the valvular lesions, and probably of infectious character, but held that these pathologic areas were in no manner connected with hypertrophy but only chanced to be concurrent. The hypertrophy<sup>21</sup> he considered as being due to the increased demands on the heart, and to be histologically expressed by increase in size and number of the muscle fibers.

Albrecht,<sup>22</sup> who studied hearts showing idiopathic hypertrophy, described much the same histologic appearances. He found increase of the connective tissue, at times changes in the arteries and dilatation and inflammation of the lymph vessels. In the muscle fibers he describes vacuoles, necrosis, double nuclei and a degeneration of the anisotropic portion of the fibrils with an increase of the isotropic portion. The sarcoplasm he considers to be increased and this he considers a progressive process. He differs from Krehl in interpreting these lesions and considers them as being not due to a secondary condition, but as actually belonging to a cycle of changes comparable to those found in inflammation of certain organs, as, for instance, the liver, in which Virchow described a hypertrophic condition of the parenchyma as the first stage of inflammation. Albrecht, therefore, regards the hypertrophy found in human hearts as the first stage of a chronic myocarditis.

Stadler<sup>23</sup> studied the changes in the hypertrophied hearts of rabbits, in which the hypertrophy has taken place as a result of experimental

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20. Krehl: *Deutsch. Arch. f. klin. Med.*, 1890, xlii, 454; 1891, xlviii, 414.

21. Krehl: *Nothnagel's Specielle Pathologie und Therapie*, vol. xv.

22. Albrecht: *Der Herzmuskel*, Berlin, 1903.

23. Stadler: *Deutsch. Arch. f. klin. Med.*, 1907, xci, 898.

valvular lesions, and again found an increase of connective tissue as well as an increase in thickness of the individual muscle fibers, this thickness being due to an increase of the sarcoplasm about the nuclei and between the fibrils, which may thus be separated. The fibrils as a rule were thickened, but at times were less thick than normally. He found many forms of nuclei, none of which appear pathologic. Vacuoles in the muscle fibers were rare.

Tangl<sup>24</sup> produced cardiac hypertrophy in rabbits by means of experimental aortic and valvular lesions and first noted hypertrophy nineteen days after producing the lesion. He found increased connective tissue, increased sarcoplasm and a number of vacuoles in the muscle fibers.

Whereas, Albrecht describes the hypertrophy as being due only to an increase in the size of the sarcoplasm, Aschoff<sup>25</sup> describes an increase in the size of the fibrils, while Letulle<sup>26</sup> speaks of increase in the number of the fibrils.

We find, therefore, essentially the same lesions in experimentally produced hypertrophy in animals, in cases of hypertrophy of the human heart found at autopsies, and in our lesions produced by the injection of adrenalin plus spartein, etc.

There is some divergence of opinion as to which part, fibril or sarcoplasm, is mainly affected by the hypertrophy; our own observations do not enable us to decide this question positively in either direction. There is also some divergence of opinion as to the correlation of the various changes found. If we return to our findings, we note undoubted progressive changes in the muscle fibers as indicated by multiplication of nuclei, besides which we find increase in the size of the muscle fibers. The early period at which these changes appear is remarkable, the increase in the size of the fibers being already present two days after the injection.

In explaining these phenomena we are tempted to make use of results obtained by Ranke,<sup>27</sup> Elizabeth Cooke<sup>28</sup> and Fletcher.<sup>29</sup> These investigators found that striated muscle which had been fatigued took up, during the period directly following the fatigue, an increased amount of water from a solution isotonic with normal muscle, the volume of the muscle increasing correspondingly. We may assume, in a similar way,

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24. Tangl: Virchow's Arch. f. path. Anat., 1889, cxvi, 432.

25. Aschoff: Verhandl. d. Gesellsch., 1905, viii, 46.

26. Letulle: Les hypertrophies cardiaques secondaires, Paris, 1879.

27. Ranke: Tetanus, Leipzig, 1865.

28. Cooke (Elizabeth): Jour. Physiol., 1898, xxiii, 137.

29. Fletcher: Jour. Physiol., 1904, xxx, 414.

as a result of the excessive amount of work done by the heart muscle following the injection of adrenalin, spartein, etc., the heart muscle takes up more water.<sup>30</sup> But from this time on the conditions in the experiments performed with striated muscle *in vitro* by Cooke and Fletcher differ from the conditions prevailing in our experiments. In the former case the muscle was kept in abnormal conditions *in vitro* and at rest; in our case the muscle remains in the body, is perfused by the normal blood and continues to perform work. This difference in the condition might explain the further changes which we found in the heart muscle in our experiments. Subsequent to the taking up of water we find a multiplication of muscle nuclei; the increase in connective tissue commences so early that we can not ascribe it to preceding parenchymatous degeneration and replacement of destroyed muscle elements. We must assume that the increased work, or the subsequent taking up of water, and perhaps a direct toxic action of adrenalin, lead to an increase in connective tissue. The later parenchymatous degenerations are probably a result of the primary swelling of the muscle fibers, and perhaps in some cases of the pressure exerted by the connective tissue.

As to the functional value of hearts which show the lesions described we shall report more fully in some other connection; here we may briefly state that such hearts are distinctly inferior to normal hearts, as we were able to demonstrate in the course of experiments on the production of edema. In this connection we may again refer to the cases in which we found dilatation of the auricles and the right ventricle evidently as the result of insufficiency of the left ventricle. Under normal conditions the animals suffering from such heart lesions do not seem to be functionally inferior to normal animals, at least in the period shortly after the injection.

In order to test which of the components of the injection were of importance, we injected in some rabbits 0.2 c.c. of adrenalin alone and in another lot larger quantities of spartein sulphate, caffein sodium benzoate or strophanthin, without adrenalin. Among 8 rabbits treated with a single injection of 0.2 c.c. of adrenalin, 3 showed a gross lesion, while 6 showed microscopic changes. In these animals the changes were of much the same character as in those injected with adrenalin and spartein, etc.; in the large majority of the cases the changes were very slight and often nothing was seen but a slight increase of connective tissue, interstitial edema and some increase in the size of the muscle fibers.

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30. Loeb (J.) (Arch. f. d. ges. Physiol., 1894, lvi, 270), believed that the hypertrophy of striated muscle following increased work over a long period came about through the taking up of water by the muscle.

Of the other rabbits, 7 received spartein sulphate, 6 strophanthin and 2 caffein sodium benzoate. After two weeks none of these animals showed any cardiac lesions, either gross or microscopic. We see, therefore, that these latter substances are powerless to produce anatomic changes.

In order to see whether a large dose of adrenalin would produce as marked a lesion as the combination of 0.2 c.c. adrenalin and spartein, etc., we injected 8 rabbits with a single dose of 0.4 c.c. adrenalin; of these, 5 showed a gross lesion, 7 showed changes on microscopic examination. The appearance of the lesions in these animals was in degree and quality the same as in the animals injected with the combined adrenalin and spartein, etc. There was increase of the connective tissue, interstitial edema, increase in the size of the muscle fibers, paleness of the cross striations, appearance of longitudinal striation, increased number of double nuclei and occasional vacuoles, also areas of dissolution of muscle fibers. We thus see that an increased dose of adrenalin acts as does a small dose of adrenalin plus caffein or spartein; or, in other words, that caffein or spartein may replace a fraction of the adrenalin, being unable, however, to replace all the adrenalin.\*

It is of interest here to note the occurrence of lesions of the aorta which followed the intravenous injection of a single small dose of adrenalin combined with spartein or caffein. In the early half of our experiments, aortic lesions were noted in 11 of 37 rabbits, while in the last 43 only 5 animals showed aortic lesions. On further analyzing this last group, only once in the last 33 animals was a lesion of the aorta noted. It has been noted that when one rabbit of a certain group from one source shows a vascular lesion, as a rule several others of this same group will also show lesions; thus, in view of the findings in the last 33 animals, we may consider that in the first lot we were dealing with a breed that were liable to spontaneous arterial disease, and that the single injection of adrenalin had little influence in producing the change in the aorta.

Considering the frequency of the occurrence of the cardiac lesions, it seems that the most marked and constant effect of adrenalin is not, as has been believed heretofore, on the blood vessels, but rather on the heart muscle. This lesion is much earlier in making its appearance, is more frequent and more constant than is the aortic lesion. Further-

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\*At the present time we do not wish to exclude the possibility that an injection of 0.2 c.c. adrenalin alone may be able to produce the same quantitative changes, although our experience indicates that lesions are not as frequent after 0.2 c.c. adrenalin.



more, we can state that the cardiac condition is not the result of a previous vascular lesion.

As to the direct causation of the heart lesion, it is very likely that excessive mechanical strain is at least one of the responsible factors. The seat of the lesion might be explained by the fact that the principal strain is experienced near the place of insertion of the muscle fibers of the left ventricle, namely, near the auriculo-ventricular junction. This may also explain the fact that the left ventricle exclusively seems to be affected. We do not, however, wish to exclude the possibility of a toxic action of adrenalin as a cooperative factor.

In conclusion, we may suggest that this method of producing lesions of the myocardium may be found serviceable in further investigations concerning the correlation between myocarditis and functional and anatomic changes in other organs.

#### SUMMARY

1. One single injection of 0.012 gm. of spartein sulphate, or 0.025 gm. caffein sodium benzoate, with 0.2 c.c. of adrenalin causes in approximately 60 per cent. of the rabbits injected myocarditic lesions of the left ventricle which are visible to the naked eye. Microscopic examination of the left ventricle in animals showing no macroscopic lesions demonstrates the presence of microscopic lesions in a still larger percentage of animals.

2. It, therefore, seems that the typical lesion produced in rabbits by the injection of adrenalin is not the aortic lesion, but this myocarditic lesion. The myocardial change is more frequent and more constant in its appearance and may be noted earlier than the arterial lesion.

3. The lesions appear a few days after the injection and consist of a combination of the following changes: (a) hypertrophy of the muscle fibers with increase in the number of muscle nuclei and indistinctness of cross striations; (b) increase in connective tissue which appears very early (there seems to be some edema present between the muscle fibers); (c) degenerative processes, affecting the muscle fibers, which become especially marked at somewhat later stages.

4. Attention is drawn to the analogy which exists between these experimentally produced lesions and the changes described in hearts showing hypertrophy, either as a result of experimental valvular lesions, or due to some common pathologic conditions in man. It is suggested that the initial phase in these changes consists in changes analogous to those described by several investigators as taking place in peripheral muscle under conditions of fatigue.

5. These lesions can not be produced through the injection of spartein sulphate, caffein sodium benzoate, or strophanthin alone; the presence of a small amount of adrenalin is necessary for their production. The typical seat of the lesion in the left ventricle near the auriculo-ventricular groove tends to confirm the suggestion that excessive strain of the heart muscle is at least one of the factors leading to these changes.

6. Hearts showing macroscopically such myocarditic lesions have been shown by us to be functionally inferior to normal hearts, when under conditions in which a surplus of work is required.

7. This easy and certain method of producing myocarditic lesions experimentally may prove of value in determining the correlation between the activity of the heart and the function of certain other organs under pathologic conditions.

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# A POSSIBLE MEANS OF DIFFERENTIATION BETWEEN CARDIAC DILATATION AND PERICARDITIS WITH EFFUSION

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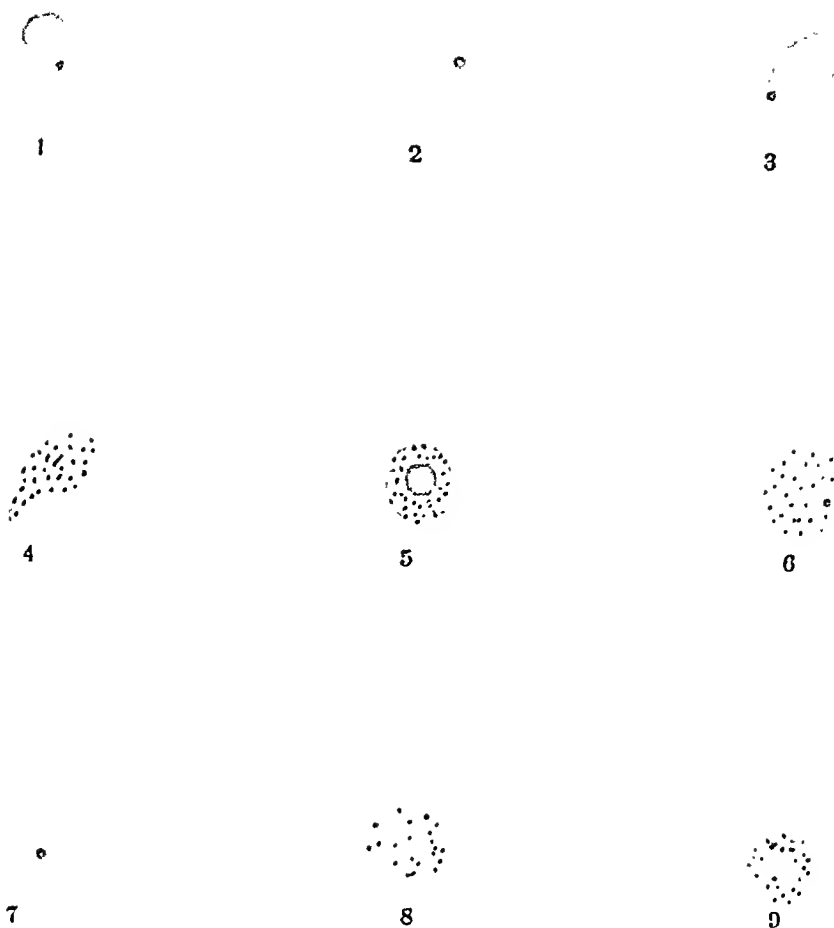
A study of the mechanics of large dilatations of the heart shows that in such conditions the right lobe of the liver is actually displaced downward, if displaced at all; but owing to displacement of the bony thorax an apparently normal or elevated position of the liver may be found. This apparently high position of the liver is likely to be found in mitral stenosis with high degree of dilatation. Here the lower anterior and lateral border of the lung is pulled upward, giving a very narrow band of relative lung-liver dulness. In large hearts the upper border of this dulness may be at the fourth rib.

In pericarditis with effusion the mechanical effect is to depress the right lobe of the liver without producing the apparent elevation; also to give a narrow band of relative lung-liver dulness, which is in a lower position than that found in dilatation of the heart. In pericarditis the beginning of the relative dulness over the right lobe of the liver may be below the sixth rib. In cardiac dilatation an apparent elevation, in pericarditis an apparent depression, of the right lobe of the liver may be found. A detailed account of the mechanics of these movements will be published later. As the mechanics of the two lesions are so different the recognition of the effects produced on the position of the liver should be of clinical value, save in very fat individuals, on whom it may be almost impossible to map out liver dulness.

In order that this point in differential diagnosis may be of greatest clinical value, an accurate knowledge of the normal position of the liver in each type of thorax is to be desired.

The point is: In cardiac dilatation high liver dulness is present: in pericarditis with effusion low liver dulness; and in each a narrow band of relative lung-liver dulness.





Figs. 1 to 6 are from three cases of pernicious anemia.

Figs. 1 and 2 show bone marrow. 1. Normoblast with nuclear particle. 2. Megalocyte with nuclear particle.

Figs. 3 to 6 show blood. 3. Nuclear particle in erythrocyte. 4. Basophilic granules in erythrocyte. 5. Basophilic granules in normoblast. 6. Nuclear particle and basophilic granules in erythrocyte.

Figs. 7 to 9 are from chronic pyrodin poisoning in the rabbit (Rabbit VII pyrodin); all from the blood. 7. Nuclear particle in erythrocyte. 8. Basophilic granules. 9. Nuclear particle and basophilic granules.

All cells were stained with methyl-green-pyronin after heat fixation, and drawn with Leitz 1/12 oil immersion, ocular No. 4.

# NUCLEAR PARTICLES IN THE ERYTHROCYTES \*

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Evidence of regeneration of the blood is of great value not only in the diagnosis, but also in the prognosis and treatment of anemias. Among the most important regenerative signs may be mentioned the occurrence of nucleated red blood cells, of basophilic granules in the erythrocytes, and of polychromatophilia. Recently I have described another manifestation of regeneration found in the human red corpuscles in anemias and in embryonic blood, and subsequent work has served to confirm the views previously expressed, with one or two exceptions.

The small, round or oval, eccentrically placed bodies, first described by Howell and later by Schmauch, in the erythrocytes of the cat, are best seen when stains are added to the fresh blood. These have been considered identical with bodies answering to the same general description morphologically found in permanent stained preparations of blood by subsequent observers—Pol, Schmidt, Jolly and myself. There are, however, differences, though it is possible that the two are closely related.

If one adds methyl green, methyl violet or other nuclear stain to the fresh blood of a normal cat, a certain number of red cells (up to about 30 per cent.) may show round, oval or irregularly-shaped structures which are deeply stained and usually situated eccentrically in the cell. They are also easily seen in fresh unstained specimens of blood, and a few of them may be found free between the red corpuscles, as Schmauch pointed out. When blood films are allowed to dry in the air, the bodies are still demonstrable for a few days on the addition of stain—and, indeed, they may be seen in the unstained, dry spreads, but in preparations kept twenty-nine days I have failed to demonstrate them, although they were very numerous in films made at the same time and examined while fresh. These bodies in the red blood cells of the cat, which stain with nuclear dyes, are, then, rather unstable. Again, fixation of the films in ethyl alcohol, methyl alcohol, alcohol and ether, and alcohol and formaldehyd (Futcher-Lazear) causes them to disappear, but short fixation in 5 per cent. or 10 per cent. formaldehyd preserves them fairly well. Underfixing the films with heat (120 degrees

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\*From the Clinical Laboratory of the Johns Hopkins Hospital.

C. for five minutes) enables one to make permanent mounts, as Schmauch has shown, but longer fixation at this temperature or thirty seconds at the spheroidal point for water will cause these very unstable bodies to disappear. I have examined the blood of six cats both before and after venesections (as much as 60 c.c. of blood withdrawn), and the results have been quite uniform in all.

While these structures in the erythrocytes of the cat are easily destroyed by heat and other methods of fixation, I have constantly found a very few characteristic "nuclear particles" in specimens of cat's blood fixed and stained in the usual manner, i. e., hematoxylin and eosin (ethyl alcohol fixation), Giemsa's stain and Hastings's stain (methyl alcohol), carbol-thionin (Fletcher-Lazear fixation), Ehrlich's triacid (heat), Pappenheim's methyl green-pyronin (heat), etc. In no other animal have nuclear particles been found in apparently normal adults, and thus far it is only in the fresh blood of the cat that these bodies described by Howell and Schmauch have been demonstrated. This, therefore, suggests a possible relationship between Howell's bodies and the nuclear particles seen in permanent blood specimens, though I can bring no further evidence of such relationship. There are, moreover, certain well-marked differences between the two: Howell's bodies, in specimens fixed for five minutes at 120 degrees C., do not stain, or stain very imperfectly, with methyl green-pyronin; nuclear particles, in thoroughly fixed smears, take a blue color, like the nuclei of normoblasts. The nuclear particles have never been found in a large proportion of the red blood corpuscles, whereas Howell's bodies may occur in 80 per cent. of the erythrocytes (Schmauch). Howell's bodies are, as we have seen, very unstable; nuclear particles, on the other hand, are demonstrable after all the usual methods of fixation, and I have found them in the blood of a patient with pernicious anemia, fixed and stained twenty-months after the films were made. Thus the two structures differ in many respects.

With the exception of the cat and the normal pregnant rat (Jolly), nuclear particles have been found in full-grown animals only during active regeneration of the blood, i. e., after severe or repeated hemorrhages, or phenylhydrazin or pyrocin poisoning, etc. They have been found in the blood of embryonic and new-born cats, mice and rats, and I have found them in the blood of the human embryo and in the most varied conditions in human adults, in whose blood other evidences of regeneration were present. As yet I have not found them in normal blood, but have observed them in nine cases of pernicious anemia (Figs. 1 to 6), in anemia in infants (two cases), in secondary anemia (two cases), in

chronic myeloid anemia (three cases), and in one patient with anemia after splenectomy had been done (splenomegaly). Furthermore, they were present in smears of the bone marrow (femur) in two cases of pernicious anemia (Figs. 1 and 2), and in one case in large numbers. It seems quite probable that they might be found in the marrow in all cases in which they are encountered in the blood. Cabot pictures multiple nuclear particles in the bone marrow, but he apparently did not find them in the blood. Within the last year Naegeli<sup>1</sup> has also "seen these (nuclear) particles very often in the blood of pernicious anemia, of embryos of animals, and in different forms of anemia."

Since they are found in the bone marrow and are almost always associated with other evidences of regeneration of the blood, nuclear particles may safely be considered a sign of regeneration. Further observation in human blood has proved the greater frequency of these particles in nucleated red cells as compared with the blood of animals. In some bloods, however, single nuclear particles in the erythrocytes may be the main evidence of regeneration; this fact was well illustrated in the case of the patient after splenectomy, in whose blood, at one time, thirty nuclear particles were found in about an hour and a half (examination with mechanical stage), while only one normoblast, no cells with basophilic granules, and a few with polychromatophilia were seen. Similarly, in the blood of a patient with pernicious anemia, kindly sent to me by Dr. C. K. Winne, Jr., of Albany, nuclear particles were numerous, but no nucleated reds were present, as he had noted. Thus, in certain instances, the chief reparative sign in the blood may be the presence of nuclear particles.

It has been urged by some<sup>2</sup> that nuclear particles are identical with the basophilic granules sometimes present in the red cells and that their classification separately is superfluous. Against this view there are striking and, I believe, conclusive facts. In the first place, it has just been shown that nuclear particles may be found in the absence of basophilic granules. They are, however, often found in the same blood and even in the same cell, as I have shown elsewhere. With modified Romanowski stains (Hasting's, Giemsa's and Wilson's) nuclear particles take the same color as the nucleus, while basophilic granules take a dark blue color. Nuclear particles are practically always round, sharply circumscribed, and eccentrically placed, and are usually single, so that it is often possible to recognize both in the same cell. But the most striking

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1. Personal communication, Nov. 6, 1908. See also article by Naegeli in bibliographic references at end of this paper.

2. Meyer (E.): Oral communication.



tinctorial differentiation is seen in preparations fixed by heat and stained with Pappenheim's<sup>3</sup> methyl green-pyronin mixture. With this stain the basophilic granules are stained a brilliant red (Figs. 4, 5, 6, 8 and 9), while the nuclear particles take on a beautiful blue color (Figs. 1, 2, 3, 6, 7, 9) like that of the nucleus (Figs. 1 to 6). Since its chromatin is densely packed, the color of the nuclear particle may be even darker than the nucleus of some of the erythroblasts. When both nuclear particle and basophilic granules are present in the same cell, the picture is very striking (Figs. 6 and 9); their separate identity is at once demonstrated. It is no more justifiable to consider them to be the same than it is to look on the nucleus of the erythroblasts and the basophilic granules as identical structures.

Many writers at present, among whom may be mentioned Meyer and Speroni, consider basophilic granules to be products derived from the nucleus of the red blood cells. That the nuclear particles is of nuclear origin there can be scarcely any doubt, for with all nuclear dyes it is stained exactly like the nucleus. In animals all transitions in size may be seen between the normoblastic nucleus and the nuclear particle, and in man the latter can be seen to be derived from the nucleus, as many preparations of blood, as well as those of the bone marrow in pernicious anemia, show. Here the nuclei can be seen broken up into two or more perfectly round, sharply circumscribed masses; the extrusion or lysis of all but one of the masses gives one the single nuclear particle seen in the bone marrow and blood. Apparently it is not necessary for the nucleus to show signs of dissolution before a nuclear particle appears in the cell, for a megaloblast with active nucleus may contain one in its protoplasm.

It is possible that the differences in staining of basophilic granules and nuclear particles is due to the presence or absence of nuclear membrane. The nuclear particle is perfectly round, as a rule, and its outline very sharply defined, resembling in every way, both morphologically and tinctorially, a miniature of pycnotic nucleus; basophilic granules are less regular and sharply defined and one gets the impression that they lie free in the cell protoplasm. If this be true, the difference in staining properties is readily explained; the reaction of the basophilic granules to stains approaches that of markedly basophilic cell protoplasm. Thus, with Romanowski stains they take a blue color instead of reddish purple, with methyl green-pyronin they are red rather than blue. Their color

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3. Boellke (Virchow's Arch. f. path. Anat., 1904, clxxvi, 47) first used this stain to differentiate nucleus and basophilic granules.

resembles that of the protoplasm of many of the lymphocytes with both of these stains. In other words, supposing basophilic granules to be remnants of the nucleus, one might explain their altered staining, provided the chromatin were no longer surrounded by nuclear membrane and its reaction were more nearly that of the surrounding protoplasm. Similarly, the characteristic staining reactions of nuclear particles might be made clear if the presence of nuclear membrane about them could be demonstrated.

## REFERENCES

- Cabot: Clinical examination of the blood, 1898.
- Howell: The life-history of the formed elements of the blood, especially the red corpuscles. *Jour. Morphol.*, 1890, iv, 57.
- Jolly: Sur la formation des globules rouges des mammifères. *Compt. rend. Soc. de biol., Paris*, 1905, i, 528.
- Jolly: Sur l'évolution des globules rouges dans le sang des embryons des mammifères. *Ibid.*, 1905, i, 593.
- Jolly: Recherches sur la formation des globules rouges des mammifères. *Arch. d'anat. microsc.*, 1907, iv, 138.
- Meyer and Speroni: Ueber punktierte Erythrocyten. *München. med. Wehnschr.*, 1906, liii, 796.
- Morris: Note on the occurrence of Howell's nuclear particles in experimental anemia of the rabbit and in human blood. *Johns Hopkins Hosp. Bull.*, 1907, xviii, 198.
- Naegeli: Ueber basophile Granulation der Erythrocyten bei Embryonen. *Folia Hæmat.*, 1908, v, 525.
- Pol: Studien zur pathologischen Morphologie des Blutes. D. I., Heidelberg, 1905.
- Schmauch: Ueber endoglobuläre Körperchen in den Erythrocyten der Katze. *Virchow's Arch. f. path. Anat.*, 1899, clvi, 201.
- Schmidt: Experimentelle Beiträge zur Pathologie des Blutes. Jena., 1902. (Cited by Pol.)

# THE SPECIFIC CHEMICAL THERAPY OF THE TRYPANOSOMIASSES AND SPIRILLOSES \*

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## OUTLINE

### TRYPANOSOMIASSES

In general. Therapy since 1904. Four groups of medicaments.

Group 1. The benzidine dyes.

Group 2. The basic tryphenylmethane dyes.

Group 3. Arsenical compounds. (Sleeping sickness.)

Group 4. Antimony compounds.

Drawbacks and dangers of treatment. Resistant strains.

Variability of trypanosomes. Combined treatment.

### SPIRILLOSES

1. Spirillosis of fowls. (South America.)

2. Spirillosis of African tick fever.

3. Spirillosis of European relapsing fever.

4. Syphilis.

## INTRODUCTION

Concerning the specific chemical therapy of the trypanosomiasesses and spirilloses so much has been published in the last few years that it would be impossible in the time at my disposal to review even a large fraction of the work that deals with these two groups of diseases. Even if time permitted, to attempt such a thing would be out of place, for as important as these diseases are in tropical countries, the American physician has only a general interest in most of them. Of necessity much will have to be omitted. In spite of this it seemed advisable to unite in one paper the therapy of these two groups of diseases, partly on account of certain analogies which exist between their etiological agents, but more particularly because some of the remedies found useful in the trypanosomiasesses have recently been applied successfully to the spirilloses. The trypanosomiasesses will be considered first.

### THE TRYPANOSOMIASSES

"Trypanosomiasis" is the general name given to a specific infection caused by microscopical protozoan organisms, trypanosoma. These dis-

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\*From Rockefeller Institute for Medical Research, New York.

\*Read before the Section on Pharmacology and Therapeutics of the American Medical Association, at the Fifty-ninth Annual Session, Chicago, June, 1908.

cases have a wide distribution and, according to Musgrave and Clegg<sup>1</sup>, destroy millions of dollars worth of animals each year. Horses, asses, cattle and a number of different animals are subject to infection. As far as we know one species only, *Trypanosoma gambiense*, is pathogenic for man. As examples of these diseases we may mention nagana (*T. brucei*), or the "Tsetse fly disease" of Zululand, surra (*T. evansi*) of India, mal de cadcras (*T. equinum*) of South America, dourine (*T. equiperdum*), formerly wide-spread in Europe, now confined almost exclusively to Algiers and to North America, and sleeping sickness (*T. gambiense*), the terrible human scourge in Africa.

*Transmission*.—In tropical countries these diseases occur in epidemic form and the trypanosoma seem to be conveyed from animal to animal chiefly by the bites of flies and fleas. In the case of dourine in the horse, however, and probably also in certain cases of sleeping sickness (Koch<sup>2</sup>), the transmission of the disease seems to be by coitus.

In general the diseases are characterized by an incubation period of variable length which is followed by fever and the appearance of trypanosoma in the circulating blood. "The mortality among most animals of economic importance is 100 per cent." (Musgrave and Clegg<sup>1</sup>).

*Therapy Before 1904*.—Prior to 1904 the most efficient medicament against the various trypanosomiasis was arsenic, and this was insufficient. In the form of arsenious acid, sodium arsenite, or Fowler's solution, it prolonged the life of infected animals by driving the trypanosomes temporarily from the circulation, but by its use cures were almost never obtained. As a rule, relapse followed relapse and eventually one had to choose between letting the animal die of the trypanosomes or of the treatment.

*Therapy Since 1904*.—This was the discouraging situation when Ehrlich and Shiga began their search for medicaments active against the trypanosomiasis. Their publication<sup>3</sup> in 1904 marks the beginning of our recent progress and stimulated greatly the experimental study of the therapy of these diseases. Workers in various laboratories took up the problem and as a result we now possess a number of medicaments far more active than the older forms of arsenic. These newer medica-

1. Musgrave (W. E.) and Clegg (M. T.): *Trypanosoma and trypanosomiasis, with special reference to Surra in the Philippine Islands*. Gov. Biolog. Lab., Rep. 5, Manila, 1903. Bureau of Public Printing.

2. Koch (R.): *Schlussbericht über die Tätigkeit der deutschen Expedition zur Erforschung der Schlafkrankheit*. Deutsch. med. Wchnschr., 1907, xxxiii, 1889.

3. Ehrlich (P.) and Shiga (K.): *Farbentherapeutische Versuche bei Trypanosomen-Erkrankung*. Berl. klin. Wchnschr., 1904, xli, 329.

ments may be conveniently divided into four groups (Table 1). 1. The benzidine dyes. 2. The triphenylmethane dyes. 3. Arsenic compounds and 4. Antimony compounds.

TABLE 1.—NEWER TRYPANOCIDAL MEDICAMENTS

## GROUP I.—BENZIDINE DYES

- 1—Trypan-red ("Trypanrot"). Ehrlich and Shiga..... 1904  
 2—Dyes of Nicolle and Mesnil. (See Table 2)..... 1906

## GROUP II.—BASIC TRYPHENYLMETHANE DYES

- 1—Malachite Green and Brilliant Green. Wendelstadt and Felmer. 1904 and 1906  
 2—Parafuchsine. Ehrlich ..... 1907

## GROUP III.—ARSENICAL COMPOUNDS

- 1—Atoxyl. Thomas ..... 1905  
 2—Acetyl-atoxyl and Paroxybenzyliden-atoxyl. Ehrlich..... 1907

## GROUP IV.—ANTIMONY COMPOUNDS

- 1—Sodium Antimonyl Tartrate. Plimmer and Thomson..... 1908  
 2—Potassium Antimonyl Tartrate. Mesnil and Brimont..... 1908

## THE BENZIDINE DYES

In the study which led to the discovery of the first of the newer medicaments active against trypanosomes, Ehrlich and Shiga chose for their investigation the virus of *mal de caderas* and studied this in white mice. The latter were selected because they were so small and cheap that the experiments could be carried out on a scale large enough to exclude experimental error, and because in them the course of the infection was so regular that even a slight variation due to a medicament could be detected. For example, Ehrlich and Shiga found that mice inoculated with their strain of *mal de caderas* died with great regularity on the fourth or fifth day. A spontaneous cure or even a chronic course of the disease in untreated animals was never observed.

*Trypan-red*.—At first Ehrlich and Shiga had almost no guiding principle to direct them in their search. They had to try far more than a hundred substances before finding one or two that possessed even a slight activity against the trypanosomes. At last, however, they came upon a red dye belonging to the benzopurpurin series which possessed a certain activity. This activity was not great; it did not cure animals infected with the disease, but it lengthened life slightly. When this dye was discovered the future problem was clearly outlined. It was necessary to increase its activity against the trypanosomes and to decrease its toxicity for the host. In this work Ehrlich found the chemist Weinberg of the greatest assistance. The latter made a careful study of the red substance, altered it chemically in many ways, and searched among the neighbors

closely related to it for compounds still more active. As a result of long, careful, scientifically directed research, another red dye was found which was far more active against mal de caderas in mice than was the original one with which Ehrlich and Shiga started. In the great majority of the cases a single injection of this new dye in the therapeutic dose, made within forty-eight hours after the inoculation of the virus, was capable of driving the trypanosomes from the circulating blood and effecting a permanent cure. From its activity against trypanosomes and its red color this new substance was named trypan-red ("Trypanrot").

*Trypan-red's Limited Efficiency.*—The finding of trypan-red did not solve the problem of the therapy of the trypanosomiasis, for it was soon discovered that the efficiency of this medicament was strictly limited. It could cure certain of the trypanosomiasis, caderas (Ehrlich and Shiga<sup>3</sup>), mbori (Laveran<sup>4</sup>) and dourine (Halberstaedter<sup>5</sup>) in mice, but against other infections in the same or in other hosts; the results, as a rule, were far from satisfying. For example, in the treatment of nagana in mice or rats a cure was almost never obtained, and the results were about as bad even in the treatment of caderas when the rat, instead of the mouse, was the host. From the limited efficiency of trypan-red it was evident that other and more powerful medicaments were needed and several workers, stimulated by the discovery of Ehrlich and Shiga, attempted to improve upon it.

*Other Benzdine Dyes.*—Nicolle and Mesnil<sup>6</sup> at the Pasteur Institute, Paris, took up the problem. They conceived the idea of submitting to a systematic study the series of colors to which trypan-red belonged, hoping in this way to obtain medicaments more active than trypan-red and seeking to determine the conditions of activity of the active compounds. In both problems they were, to a certain extent, successful. They found a number of colors which were more active against some species of the trypanosomes than trypan-red, and determined a few of the conditions of activity.

*Table 2.*—Compiled from the work and tables of Nicolle and Mesnil,<sup>6</sup> Table 2 shows the curative activity of the benzdine dyes against the try-

4. Laveran (A.): Le trypanroth dans le traitement de quelques trypanosomiasis. Compt. rend. Acad. d. sc., Paris, 1904, cxxxix, 19.

5. Halberstaedter (L.): Untersuchungen bei experimentellen Trypanosomen-Erkrankungen. Centralbl. f. Bakteriologie u. Parasitenk., Orig., 1905, xxxviii, 525.

6. Nicolle (M.) and Mesnil (F.): Traitement des trypanosomiasis par les couleurs de benzdine, Première partie—étude chimique. Ann. de l'Inst. Pasteur, 1906, xx, 417; Seconde partie, étude expérimentale. Ann. de l'Inst. Pasteur, 1906, xx, 513.



panosomes of surra, caderas and nagana in mice. These animals were treated only after the typanosomes were visible in the blood and as a rule each animal received only one injection of the given medicament.

TABLE 2.—BENZIDINE DYES.\*

Chemical Composition.	Symbols of Nicolle and Mesnil.	Color of Solution.	Dose in cc. for Mouse of 15-20 gm.	Three species of Trypanosomes Treated.	Mice.	
					Number Treated.	Number Cured.
Amidonaphtol disulphonic acid, 1. 8. 3. 6. + dichlorbenzidine. (Alk.)†	Cl.	Violet blue.	1.	{ Surra of India. Mal de Caderas. Nagana.	5 4 10	4 2 3
Amidonaphtol disulphonic acid, 1. 8. 3. 6. + tolidine. (Alk.)† (Trypanblau or trypan-blue.)	A	Blue . . . .	1.	{ Surra of India.‡ Mal de Caderas. Nagana.	15 26	1 5
Amidonaphtol disulphonic acid, 1. 8. 3. 6. × tolidine. (Alk.)† (Trypanblau or trypan-blue.)	A	Blue . . . .	1.	{ Surra of India.‡ Mal de Caderas. Nagana.	6 9	1 3
Naphtylamine disulphonic acid, 2. 7. 3. 6. + benzidine.	Alpha	Deep cherry red.	.75	{ Surra of India.§ Mal de Caderas. Nagana.	5 13	1 3
B. Naphtylamine disulphonic acid, 2. 3. 6. + benzidine orthomonosulphonic acid (Trypanrot or trypan-red.)	T	Cherry red.	.50	{ Surra of India. Mal de Caderas. Nagana.	7 14 13	3 6 1
Amidonaphtol disulphonic acid, 1. 8. 3. 6. + para-diamidodiphenylurea. (Alk.)†	Ph.	Violet . . .	1.	{ Surra of India.§ Mal de Caderas. Nagana.	4 15	0 1

\*For details and for the chemistry of these compounds the work of Nicolle and Mesnil<sup>6</sup> should be consulted. A shorter account of the chemistry of these dyes is given in English by Wenyon<sup>7</sup> and another by Nabarro.<sup>8</sup>

7. Wenyon (C. M.): Action of the colors of benzidine on mice infected with *Trypanosoma dimorphon*. Jour. Hygiene, Cambridge, 1907, vii, 273.

8. Nabarro (D.): Trypanosomes and trypanosomiasis. Trans. from the French of Laveran (A.) and Mesnil (F.). Chicago, 1907, W. T. Keener & Co.

† (Alk) indicates that the union of both side-chains to the base was effected in an alkaline medium.

‡ Action of the medicament "doubtful."

§ Action of the medicament "insufficient."

## BASIC TRIPHENYLMETHANE DYES

*Malachite Green and Brilliant Green.*—Following the discovery of trypan-red by Ehrlich and Shiga, Wendelstadt and Fellmer published their investigations. These had resulted in finding that malachite green<sup>9</sup> and brilliant green,<sup>10</sup> basic dyes of the triphenylmethane series, were active against trypanosomes. Even when given in very small quantities these new dyes caused the trypanosomes of nagana to disappear from the blood of rats. Unfortunately the results were not permanent. In one case life was prolonged to the seventy-second day, but by the use of these dyes alone no cures were effected.

Besides being insufficient to effect cures, the dyes of Wendelstadt and Fellmer were capable of setting up violent inflammatory processes when introduced into the tissues. For this reason in their experiments these authors usually injected malachite green into the tails of rats, believing that these animals could bear the loss of large portions of the tail easier than they could extensive areas of skin.

*Parafuchsin.*—Many attempts to find more active medicaments belonging to the triphenylmethane series have been made. After extensive experimentation Ehrlich<sup>11</sup> has concluded that parafuchsin is probably the most active known representative of this series. By repeating several times the subcutaneous injection of this medicament Ehrlich has effected a certain number of cures in mice infected with nagana. Unfortunately, even with parafuchsin, repeated injections are apt to lead to necrosis or sloughing of the skin.

*Parafuchsin Feeding.*—To avoid these unpleasant sequelæ, Ehrlich attempted to introduce the drug in a different way, namely, by mouth. To do this certain technical difficulties had to be overcome, for when cakes that had been soaked in parafuchsin were offered to mice Ehrlich found that the taste of this medicament was so disagreeable to these animals that they would starve to death before they would eat them. To obviate this difficulty before incorporating it into cakes Ehrlich heated the parafuchsin with an excess of oleic acid, converting it into a compound that was readily absorbable from the intestine, yet one that

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9. Wendelstadt (H.): Ueber die Wirkung von Malachitgrün und anderen verschiedenartigen Stoffen gegen Nagana—Trypanosomen bei weissen Ratten. Deutsch. med. Wchnschr., 1904, xxx, 1711.

10. Wendelstadt (H.) and Fellmer (T.): Ueber Einwirkung von Brilliantgrün auf Nagana-Trypanosomen. Ztschr. f. Hyg. u. Infectiouskrankh., 1905, lii, 263.

11. Ehrlich (P.): Chemotherapeutische Trypanosomen-Studien. Berl. klin. Wchnschr., 1907, xlv, 233, 280, 310, 341.



was no longer distasteful to his animals. After quickly becoming accustomed to the new parafochsin oleate cakes, mice readily accepted them and lived on these alone for months at a time.

*Prophylactic Action.*—Ehrlich found that parafochsin given in this form had a very strong prophylactic action. For example, mice almost never became infected with nagana if they were fed on parafochsin cakes for some days both previous and subsequent to the inoculation of the virus. Furthermore, they rarely became infected if the feeding was commenced simultaneously with the introduction of the virus.

*Curative Action.*—The curative action of the parafochsin was not pronounced. If the feeding of mice infected with nagana was begun as late as twenty-four hours after the introduction of the virus the cures effected were rare exceptions.

#### THE NEWER COMPOUNDS OF ARSENIC

The third group is that of the arsenical compounds. As we have already stated, the older forms of this medicament were insufficient. It is not to these but to the newer forms, atoxyl and its derivatives, that I wish to direct attention.

*Atoxyl.*—Atoxyl is the sodium salt of paramidophenyl arsenic acid and contains 24.1 per cent. of arsenic<sup>11</sup>. It had been used for about three years in the treatment of skin diseases and anemias before its action on diseases caused by the trypanosomes was known. Its introduction into the therapy of the trypanosomiasis by Thomas<sup>12</sup> in 1905 marks a great advance in our attempts to cure these diseases.

*The Advantage of Atoxyl.*—Compared with the older arsenical preparations atoxyl possesses several distinct advantages. One of these is its slight toxicity. According to Blumenthal<sup>13</sup> atoxyl is 1/40 as toxic as Fowler's solution. Another advantage is that injections of the newer compound are less painful and irritating and are said not to lead to sloughing of the skin. Most important of all, however, is the fact that the improvement which is noted after the use of the drug is far more apt to be permanent. In the treatment by atoxyl of various animals infected with the organisms of nagana, surra, mal de caderas, dourine

12. Thomas (H. W.): Some experiments in the treatment of trypanosomiasis. Brit. Med. Jour., 1905, i, 1140.

13. Blumenthal (F.): Ueber Metarsensäureanilid (Atoxyl) Med. Woche, 1902, iii, 163.

and sleeping sickness, Thomas,<sup>12, 14</sup> Uhlenhuth,<sup>15</sup> Nicolle and Mesnil,<sup>6</sup> Yakimoff,<sup>16</sup> Ehrlich,<sup>11</sup> Browning,<sup>17</sup> and others seem to have effected a certain number of definite cures.

*Rapid Action of Atoxyl.*—When injected in the proper therapeutic dose into animals infected with trypanosomes the action of atoxyl is usually rapid. In a number of cases Thomas<sup>12</sup> found involution forms in the blood of the infected animals four to six hours after the administration of the drug, and by the eighteenth hour all the organisms had disappeared. While this may be regarded as the common course of events, exceptionally the injection of this medicament is less effective. Out of 105 mice infected with the organisms of nagana and receiving only a single injection of atoxyl, Browning states that from the blood of twenty-four of these the trypanosomes never disappeared and the animals died of the disease.

*Prolonged Treatment With Atoxyl.*—In the treatment of the various trypanosomiasis by atoxyl the best results have been obtained by giving the drug repeatedly over a long interval of time. Thomas and Breinl,<sup>14</sup> who have tested the drug on a large number of animals infected with various trypanosomes, state that it is necessary to continue the administration of the medicament after all the favorable signs are present. As a rule they gave one or more injections each week for one to three months. In spite of this seemingly thorough treatment, from a report by Breinl and Todd,<sup>18</sup> it would seem that a certain number of the animals which Thomas and Breinl regarded as cured afterward had relapses and died of the disease. The experience of those who have tested the drug most thoroughly indicates that a single injection of atoxyl is rarely sufficient and that even when numerous injections are made over a long period of time in many cases cures are not effected.

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14. Thomas (H. W.) and Breinl (A.): Report on trypanosomes, trypanosomiasis and sleeping sickness, being an experimental investigation into their pathology and treatment by H. W. Thomas, and a description of the tissue changes by A. Breinl. Mem. 16, Liverpool Sch. Trop. Med., Liverpool, 1905, Williams and Norgate.

15. Uhlenhuth, Gross and Bickel: Untersuchungen über die Wirkung des Atoxyls auf Trypanosomen und Spirochäten. Deutsch. med. Wchnschr., 1907, xxxiii, 129.

16. Yakimoff (W. L.): Zur Behandlung der Dourine. Therapeutische Versuche mit Trypanrot an Laboratoriumstieren. Centralbl. f. Bakteriologie u. Parasitenk., Orig., 1907, xlv, 437.

17. Browning (C. H.): Experimental chemotherapy in trypanosome infections. Brit. Med. Jour., 1907, ii, 1405.

18. Breinl (A.) and Todd (J. L.): Atoxyl in the treatment of trypanosomiasis. Brit. Med. Jour., 1907, i, 132.

*Atoxyl and Sleeping Sickness.*—Although atoxyl has been shown to possess a certain value in the treatment of experimental trypanosomiasis, its claim to our attention is derived less from this than from its importance in the treatment of human trypanosomiasis, or sleeping sickness. As a remedy against this infection practically all observers are agreed that atoxyl is the best medicament yet tried.

*The Administration of Atoxyl.*—Concerning the proper dose and the proper method of administering atoxyl there has been a great diversity of opinion. A discussion of these differences can not be entered into here. It seems more profitable to give instead the conclusions of Robert Koch,<sup>2</sup> whose experience with this medicament in the treatment of sleeping sickness is far greater than that of all the other investigators combined.

*The Dose.*—According to Koch the proper dose of atoxyl in the treatment of human beings is 0.5 gm. In the case of sleeping sickness to use less is to delay the cure and to invite failure. To use more is dangerous, as Koch discovered when at one time he injected doses varying between 0.5 and 1 gm., hoping by this means to hasten the cures. In some of the patients that received these larger doses Koch soon observed a symptom he had never seen in untreated patients or in those that had received only 0.5 gm. This was a blinding, which in a comparatively short time developed in both eyes. In the beginning it was hoped that this symptom might be only temporary, but in Koch's patients, unfortunately, no improvement appeared and they remained permanently blind. As soon as Koch became convinced that the blinding was due to atoxyl the large doses were immediately reduced to 0.5 gm. and no other cases of blindness developed. In this connection it is interesting to note that the larger doses of atoxyl gave no better results than did the 0.5 gm. doses.

*The Double Dose.*—The 0.5 gm. of atoxyl is given by Koch on each of two succeeding days. In his experience this method has been much more effective than the injection of a single 0.5 gm. In one case in which only a single injection of this amount was given, the trypanosomes reappeared in the blood after only five days. On the other hand, where the double injection was given the trypanosomes were much later in reappearing.

*Double Injections Repeated.*—With suitable intervals between, the double injections must be repeated many times to effect a cure. After extensive experimentation the method that Koch finally adopted gave excellent results. It is as follows: Half a gram of atoxyl is injected subcutaneously or intramuscularly on each of two succeeding days, and.

with intervals of ten days between, this double treatment is repeated for many months.

*Internal Administration of Atoxyl.*—With the internal administration of atoxyl Koch has had no success. The 0.5 gram dose given by mouth was found to be insufficient, as in about 30 per cent. of the cases the trypanosomes returned during the treatment. On the other hand, larger doses than this could not be used, as they called forth toxic symptoms just as similar doses had done when injected subcutaneously or intramuscularly.

*Sleeping Sickness.*—Before taking up the results obtained with atoxyl in the treatment of sleeping sickness a few words about the disease may not be out of place. Sleeping sickness is the name applied to the infection produced in human beings by *Trypanosoma gambiense*. The name, however, while aptly fitting the last stages of the infection is not at all descriptive of the earlier ones, in which the enlargement of the cervical glands may be the only objective sign. Nevertheless an early diagnosis of the infection can easily be made by puncturing one of the enlarged glands and examining its contents microscopically. In this way the trypanosomes are so readily detected by skilled observers that Koch<sup>2</sup> reports finding them in 347 out of 356 glands examined.

*Koch's Classification.*—In order to make clear the action of atoxyl on his sleeping sickness patients, Koch found it desirable to divide those who came for treatment into two classes, the "slightly ill" and the "severely ill." In the slightly ill the only objective sign was the enlargement of the lymph glands, with the presence in these of trypanosomes. The patients felt unwell and complained of weakness, especially in the lower extremities. They often had pains in the head, breast or limbs. In these patients the duration of the disease varied from one month to a year or more. In the severely ill objective signs became prominent. The weakness that was previously subjective now often manifested itself in a trembling of the limbs, a dragging of the feet or a tottering gait. As this weakness became more and more marked the patients passed successively through the stages in which they walked alone with difficulty, then with a stick, and at last only when supported on both sides. Finally they could neither stand nor sit without being supported, consciousness was lost and death seemed close at hand.

*The Slightly Ill.*—The best results that Koch has had were obtained in the treatment of his first class, the slightly ill. Following the injections of atoxyl the trypanosomes disappeared promptly from the circulating blood and from the lymph glands, and the enlarged glands decreased in size until after sixty days, as a rule, they were no longer

palpable. The symptoms of the disease were also favorably influenced, but the improvement here was slower in making its appearance. It was usually not noted until three or four weeks after the commencement of the treatment. The patients then began to feel better, their pains decreased and disappeared, their strength returned and they were again able to walk and work without inconvenience. In cases of this class Koeh<sup>2</sup> believes that a cure can be effected in four to six months.

*The Severely Ill.*—The results of the treatment of the severely ill have not been so good. This class was a large one and contained a number of patients that were desperately ill. When brought for treatment some were unconscious and apparently had only a short time to live. Under the influence of the atoxyl treatment, however, a number even of these have improved so much that they can again walk without assistance. Not a few have apparently been cured, their health remaining good during the ten months they have been under observation. Nevertheless the mortality has been high. Of the 374 patients 78, or 22.9 per cent., are already dead. This 78, however, includes a number that were so near death's door when they arrived that they lived to receive only 1 or 2 injections. If the patients that were insufficiently treated were excepted the death rate in this class would be only about half of what is here recorded. Comparing the mortality of the treated with that of untreated patients during a similar interval of time, Koch finds that the former is only a tenth or twentieth of the latter.

*The Native.*—The results obtained by Koeh will be better appreciated if some of the characteristics of his patients, the African natives, are mentioned. Although in the beginning the negro is anxious to be treated, he makes a very bad patient. In order that the treatment may be successful it should be given for a long time, at frequent intervals, and in maximum doses. The negro, however, is not disposed to undergo a prolonged course of treatment. As soon as he feels a little better or becomes tired of the treatment he is apt to run away. Neither will he stand much pain. Since the internal administration of atoxyl has proved to be insufficient, this medicament is always given hypodermically. At times a single injection given in this way is sufficient to cause the negro to remain away for months before returning for a second injection. In the case of the colors, the injection of which is evidently quite painful, the dose can not be regulated by what is therapeutically necessary, but by the amount the patient will stand. So it comes about that in not one of the 1,633 patients that Koch has had has he been able to administer the treatment exactly as he would have liked.

With such patients to treat the results Koeh has obtained are all the more remarkable.

*Caution.*—In spite of the favorable results of Koeh, it is impossible at present to know whether or not any of his patients have been cured. It is true that no signs of a relapse have appeared in the patients he has treated for ten months, but this interval is entirely too short to enable us to conclude that the patients are cured. After two months of treatment some of the patients appeared cured, and the treatment was interrupted. The relapses that followed showed that a cure had not been effected.

*Kopke's Unfavorable Results.*—In this connection we should recall the results of Ayres Kopka,<sup>19</sup> whose experience in the treatment by atoxyl of sleeping sickness is longer, if not so extensive as that of Koeh's. In spite of the fact that Kopke has used large doses of atoxyl and has administered the drug for many months, his results have been distinctly unfavorable. Of his ten patients this investigator in 1906 reported having lost six.

In a later report<sup>20</sup> Kopke gives the results of treating twenty-eight blacks and one white man. Of the twenty-nine only six were still living. For two of the latter the treatment had been stopped, in one case for a short while only, in the other for nine months. At the time of the report the last-mentioned patient was afflicted with partial blindness as a result of the treatment. Two of those that died had been treated for over a year, one for fifteen, the other for twenty-one months. In this time the first had received 39, the second 54 grams of atoxyl. In spite of the large quantity of the medicament that had been administered, trypanosomes were found in the fluid withdrawn from these two patients at the last lumbar punctures made before their death.

*Acetyl-Atoxyl and Paroxybenzyliden-Atoxyl.*—Until recently atoxyl was our most efficient arsenical preparation. Thanks to Ehrlich, however, we now possess two other medicaments which, while containing about the same percentage of arsenic as atoxyl, are, for the mouse, only one-tenth as toxic. These preparations are acetyl-atoxyl and paroxybenzyliden-atoxyl, and in experiments on nagana in mice they have been found more than ten times as efficient as atoxyl. For example, Browning,<sup>17</sup> in Ehrlich's laboratory, treated sixty-four mice with atoxyl. Of these, five, or a little less than 8 per cent., were cured. Under similar

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19. Kopke (Ayres): Trypanosomiasis humaine. xv Cong. internat. de méd., Lisbon. Section xvii, 1906, 233.

20. Kopke (Ayres): La maladie du sommeil. Ber. u. d. xiv Internat. Kong. f. Hyg. u. Demographie, Berlin, Sept. 23 to 29, 1907, iii, 720.

conditions 33 nagana mice were treated with the newer preparations and 31, or 93 per cent., were cured.

According to Browning<sup>17</sup> these two newer preparations are the most efficient therapeutic agents known in the treatment of nagana infections in mice. If the treatment is instituted twenty-four hours after the infection begins, this investigator states that practically a certain cure can be effected with a single injection of these medicaments.

*The Time of Intervention.*—The results of treatment with these newer preparations indicates that the earlier the treatment is begun the better chance there is of effecting a cure. As has already been stated, Browning has found that he can effect a cure in practically all cases of nagana in mice by employing acetyl-atoxyl or paroxybenzyliden-atoxyl if the treatment is begun within twenty-four hours after the introduction of the virus. If, on the other hand, he waited until forty-eight hours after the infection commenced he found that a single injection of these medicaments no longer sufficed to effect a cure. Of eight mice treated in this way all died of the infection. In order to effect cures at this late stage of the infection—twelve to eighteen hours before the expected death of the mouse—Browning<sup>17</sup> found it necessary to resort to repeated injections of the medicaments, and even then only about half of the animals were cured. Thus, in the treatment of 22 mice, by repeating the injections three to five times in each case, Browning cured 12, or 55 per cent., of them.

So strikingly good are the results obtained with acetyl-atoxyl and paroxybenzyliden-atoxyl in the treatment of mice that it seems incumbent on us to test these drugs wherever atoxyl has been found of value. In the beginning, however, one should proceed with great caution. It is not permissible to conclude that in other species of animals the results will be equally good, merely because favorable results have been obtained in the treatment of mice. In fact, Ehrlich<sup>11</sup> has already determined that these medicaments vary greatly in their toxicity according to the species of animal treated. For the mouse, in which such brilliant results have been obtained, these newer preparations are peculiarly non-toxic. Unfortunately the same can not be said of their action on the horse and the guinea-pig.

#### ANTIMONY COMPOUNDS

A fourth group of medicaments active against the trypanosomes has recently been introduced. This is the group of the antimony compounds. The most active member of this group that Plimmer and Thomson<sup>21</sup>

21. Plimmer (H. G.) and Thomson (J. D.): Further results of the experimental treatment of trypanosomiasis in rats; being a progress report of a committee of the Royal Society. Proc. Roy. Soc., London, No. B, 536, 1908, lxxx, 1.

have tested is sodium antimonyl tartrate. From their work on rats infected with the organisms of surra and nagana this medicament is regarded by these writers as superior to atoxyl. Its action on the trypanosomes is decidedly quicker. After its administration, at times within one-half hour, and usually within two hours, the trypanosomes disappear completely from the peripheral circulation, although they may have been numerous when the injection was made. Of thirty-nine animals treated with sodium antimonyl tartrate the majority were living fifty-two days later. Unfortunately this interval is too short for us to draw from it any definite conclusions.

Independent of Plimmer and Thomson and before the publication of their paper, other investigators turned their attention to the antimony compounds. Mesnil and Brimont,<sup>22</sup> working with potassium antimonyl tartrate, found that the injection of the therapeutic dose of this medicament usually caused the trypanosomes to disappear from the peripheral circulation of the infected animals in about two hours. In many cases, however, the disappearance was only temporary, the percentage of cures effected varying with the organisms causing the infection. With mice infected with surra of India, surra of Mauritius and dourine these investigators have been able to effect cures in the majority of the cases after a single injection of the medicament. On the other hand, in the treatment of animals infected with the organisms of mal de caderas, Gambian horse sickness, sleeping sickness and two species of nagana, the results have been much less satisfactory.

#### DRAWBACKS AND DANGERS

In attempting to solve a problem as difficult as that of the therapy of the trypanosomiasis, it seems almost inevitable that many substances should be tried which eventually will have to be abandoned. While the dyes, or colors, were the medicaments with which our first successes in the treatment of the trypanosomiasis were attained, the drawbacks attending the use of most of these are so great that we are inclined to think they will play a minor rôle in the therapy of the future.

*The Dyes.*—In addition to imparting a bright, unnatural color (red, blue or violet) to the skin and mucous membranes, the subcutaneous injection of the dyes seems to be quite painful and, in a certain number of cases, leads to induration or sloughing of the skin, to nephritis, or to

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22. Mesnil (F.) and Brimont (E.): Sur l'action de l'émétique dans les trypanosomiasis, note préliminaire, Bull. de la Soc. path. exotiq., 1908, i, 44; Sur la valeur curative de l'émétique dans les diverses trypanosomiasis, *ibid*, 212.



a chronic intoxication which may bring about the death of the animal long after the infection with the trypanosomes has apparently been cured.

*Atoxyl*.—As valuable as atoxyl has proved to be in the treatment of sleeping sickness, in the use of this medicament too much care can not be exercised. It has been clearly and repeatedly demonstrated that large doses of this drug may lead to permanent blindness. Twenty-two of Koch's 1,633 patients lost their sight and Kopke's experience has been relatively much worse. Of 29 patients treated 6 had ocular trouble and in 4 the blinding was complete. Fortunately for the future of the atoxyl therapy it seems that the blinding effect of this drug may be avoided by paying scrupulous attention to the dosage. In Koch's vast experience, loss of vision was observed only in those that received injections of more than 0.5 gram.

*Acetyl-Atoxyl*.—While in no way wishing to suggest that larger animals and man will behave under medication as mice and rats do, I should like to call attention to a phenomenon in these animals which is curious, persistent and little understood. Ehrlich<sup>11</sup> was the first to notice that, when mice were treated with acetylatoxyl, not infrequently their characteristics became profoundly altered. Following therapeutic injections of this medicament in a certain number of cases these animals were converted into dancers or waltzers resembling strikingly the long-known Japanese waltzing mice. Round and round in their jars they would spin, first in one direction and then in the other. When once the dancing habit was acquired it usually persisted until the death of the animal. Often this did not occur until many months afterward.

#### RESISTANT STRAINS

One of the most interesting and important recent discoveries in connection with the trypanosomes is, that these organisms can acquire a marked resistance to medication. This resistance was first suspected by Ehrlich<sup>11</sup> in mice infected with nagana and treated with parafochsin cakes. Occasionally after the feeding was discontinued relapses occurred. In such cases, if the feeding was again resorted to, the trypanosomes disappeared from the circulation, but tended to reappear after the feeding was stopped. In some cases, with each successive relapse, the parasites yielded less and less readily to treatment, until a time finally came when the trypanosomes could no longer be driven from the circulation by the parafochsin. Ehrlich concluded that one of two things had occurred. Either the organism of the mouse had acquired the power of

rendering the parafochsin harmless or the trypanosomes had become resistant to this medicament. A simple experiment showed that the latter hypothesis was the correct one. Into a normal mouse trypanosomes which no longer responded to treatment were inoculated and feeding with parafochsin was instituted. It was found that this medicament was no longer able to drive the trypanosomes from the circulation. Mice infected with these organisms died in spite of treatment. The virus had acquired a new characteristic. A race of trypanosomes resistant to parafochsin had been produced.

*A General Phenomenon.*—That parafochsin was not the only drug against which trypanosomes could be rendered resistant was soon evident. By means of the principle of insufficient treatment, races of trypanosomes have been produced which are resistant to several different medicaments. In the preparation of these feeding was usually resorted to, but in the case of medicaments not easily absorbed from the alimentary tract (trypan-red and trypan-blue, for example), these were injected in small quantities hypodermically, the doses being chosen so as to prolong life without rendering the blood free from the parasites. In this way races of trypanosomes have been produced which are resistant to one or more members of the four groups of medicaments now known to be active against trypanosomes. It seems possible to Ehrlich that we are here dealing with a general phenomenon, and that we will probably be able to obtain races resistant to other groups of trypanocidal chemicals, if, as is to be expected, these shall be found.

*Persistence of Resistance.*—When resistance to medication has once been acquired it tends to persist for an indefinite time. In Ehrlich's laboratory it has been found that a race of trypanosomes resistant to fuchsin retained its resistance to this medicament after passing through twenty-five normal mice. On testing the same strain after the fortieth passage, however, it was found to be no longer resistant. Similarly a strain of trypanosomes resistant to atoxyl at the end of six months was found to have lost its resistance after seven and three-fourths months (eighty-seventh passage). Some strains, on the other hand, have as yet shown no signs of losing their resistance.

Browning<sup>17</sup> reports that a strain resistant to atoxyl retained its resistance after passing through 140 normal mice in the course of fourteen months.

*Behavior Toward Other Medicaments.*—A race of trypanosomes resistant to one medicament is usually resistant to certain other closely related medicaments. For example, trypanosomes that have become

resistant to atoxyl acquire at the same time more or less resistance to acetyl-atoxyl and to paroxybenzyliden-atoxyl, and races resistant to trypan-red become in the same way resistant to trypan-blue. Nevertheless a race of trypanosomes resistant to one medicament or to a group of medicaments is not resistant to all. Toward medicaments of other groups (Table 1) it seems to acquire no resistance, being as susceptible to treatment with these as was the original species from which the race was developed. For example, trypan-red resistant races are not at all resistant to para-fuchsin or to atoxyl, and atoxyl-resistant races show no resistance to trypan-red or to para-fuchsin.

*Multiple Resistant Races*—When a race of trypanosomes becomes resistant to a medicament, or to a group of these, its ability to acquire a resistance to other medicaments seems to be in no wise altered. Races of trypanosomes having a double and even a triple resistance have been produced. After having been first rendered resistant to atoxyl a strain of trypanosomes acquired a resistance to trypan-blue and then to para-fuchsin. In this way a single strain of trypanosomes finally came to possess a strong resistance to all three of the groups of medicaments at that time known to be active against trypanosomes.

*Natural Variability of Trypanosomes*.—It is important to realize that the characteristics of trypanosomes are more or less variable and unstable. As we have already seen, under the influence of prolonged and insufficient treatment they easily acquire a resistance to the medicament used. This resistance may be completely lost in the course of a few months, or it may be preserved for a very long time, possibly for years. In addition to these acquired variations certain others have been noted in organisms that have never previously been subjected to treatment. If one attempts to treat a given species of the trypanosomes with a certain medicament, at one time the organisms may appear highly resistant, at another very susceptible. To distinguish these two phases Ehrlich<sup>11</sup> proposes to call the race resistant to treatment *tenax*, that susceptible to treatment *debilis*. At times the simple passage of the trypanosomes through a rabbit suffices to convert a resistant (*tenax*) strain into a non-resistant (*debilis*) strain.

According to Ehrlich, the terms *tenax* and *debilis* have nothing to do with the virulence of the organisms. They refer merely to the resistance of the parasites toward a specific medicament. In one case an original nagana strain was separated into two strains, one of which was *tenax*, the other *debilis* to trypan-red. Nevertheless, for animals these two strains were found to be equally pathogenic.

## COMBINED TREATMENT

If the curing of cases that experience has shown are difficult of treatment be taken as the test of efficiency, probably the best results thus far obtained in the various experimental trypanosomiasis have been secured by means of combined treatment. By combined treatment is meant the simultaneous or alternate use of two or more medicaments or methods of administration.

The value of thus associating two remedies in the treatment of experimental trypanosomiasis was early pointed out by Laveran. By injecting arsenious acid and following this up twenty-four hours later with trypan-red Laveran<sup>4</sup> was able to effect definite cures where either of the medicaments used alone always failed.

*Atoxyl and Mercury.*—In the treatment of nagana in rats Moore, Nierenstein and Todd<sup>23</sup> report having recently combined with marked success injections of atoxyl with those of the bichlorid of mercury. By giving atoxyl and then, after the trypanosomes had disappeared, injecting large doses of the bichlorid of mercury, these workers found that, of twenty-five rats thus treated, seventeen survived, apparently cured. The cause of death of four was unknown. Two were sacrificed and their organs were examined with negative results. Only two died of the trypanosomes. This result is all the more striking when we note that, of the fourteen rats used as controls and treated with atoxyl alone, not one was cured.

*Acetyl-Atoxyl and Atoxyl-feeding.*—One of the most striking examples of the value of combined treatment is furnished by Browning.<sup>17</sup> Into each of eleven mice richly infected with nagana Browning injected 0.025 gm. of acetyl-atoxyl, and the next day began to feed these animals on biscuit containing atoxyl. The feeding was continued for ten or eleven days. Of the eleven animals thus treated, ten were permanently cured. With the same strain of trypanosomes and at a similar late stage in the infection, control experiments by the same author indicate that repeated injections of the acetyl-atoxyl would have saved only 55 per cent. of these animals, while, if the medicament had been given only once, none of them would have been cured.

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23. Moore (B.), Nierenstein (M.) and Todd (J. L.): On the treatment of trypanosomiasis by atoxyl (an organic arsenical compound), followed by a mercuric salt (mercuric chlorid), being a biochemical study of the reaction of a parasitic protozoon to different chemical reagents at different stages of its life-history. *Bio-Chem. Jour.*, 1907, ii, 300.

## THE SPIRILLOSES

From the treatment of the trypanosomiasis we now turn to that of the spirillosis. The term "spirillosis" is used in a general sense and means an infection caused by spiral organisms. The spirilloses, therefore, include infections with a variety of organisms, spirilla, spirochetes and treponemas. The only diseases that we shall take up here will be the South American spirillosis of fowls, African tick fever, European recurrent fever and syphilis. With the exception of the first, man is subject to all of these.

*Treatment of the Spirilloses.*—Uhlenhuth<sup>15</sup> was the first to apply to one of the spirilloses treatment found effective among the trypanosomiasis. In so doing he was influenced by the analogy which exists between trypanosomes and spiral organisms, and especially by the view of Schaudinn, that certain spirochetes represent special developmental stages of trypanosomes.

## THE SPIRILLOSIS OF FOWLS

The spirillosis of fowls was the first of these diseases successfully treated. According to Uhlenhuth,<sup>15</sup> this spirillosis begins with a high fever and diarrhea and often terminates in a fatal septicemia. The cause of the disease, *Spirillum gallinarum*, was discovered by Marehoux and Salimbeni in Rio de Janeiro in 1903. It is conveyed from chicken to chicken in nature by a small tick, *Argas miniatus*. In untreated experimental animals, the spirilla appear in the blood on the second day after inoculation, increase in number until the fourth to the sixth day, when they are present in very large numbers. On the seventh to the ninth day the crisis occurs, the organisms suddenly disappear from the circulation, and the animals that survive are immune. A natural immunity is seldom encountered. In inoculating forty fowls, Uhlenhuth found it only twice.

*Atoxyl and the Spirilloses of Fowls.*—The drug that Uhlenhuth<sup>15</sup> found most efficient in the spirillosis of fowls was atoxyl. As a rule, it was injected intramuscularly, the usual dose for a chicken being 0.25 gm. When used in this way the drug was found to exercise both a preventive and a curative action. If, for example, the atoxyl was injected into infected fowls before the appearance of the spirilla, these organisms were never found by examining fresh specimens of blood. If, on the other hand, the drug was used curatively, being injected much later, at a time when the spirilla were present in large numbers, these disappeared in twenty to thirty hours, while the blood of the controls

still teemed with the organisms. The use of atoxyl, either preventively or curatively, was followed by a lasting immunity.

*Slow Action of Atoxyl.*—Although atoxyl may be used prophylactically and curatively, in neither case does the drug bring about an immediate and complete extermination of the parasites. For a few days following the injection of the medicament, the parasites are present in scanty numbers in the blood of the treated animals and may be detected by injecting the blood into susceptible animals or by carefully searching well-stained specimens of the blood.<sup>24</sup> Even when atoxyl is mixed with the virus previous to the injection, the blood of animals receiving the mixture is infectious for other animals one, two and even three days after the injection.<sup>25</sup>

*Determining the Therapeutic Dose.*—In determining the maximum quantity of atoxyl that may be used in the treatment of animals infected with *Spirillum gallinarum*, it is not always safe to rely on results obtained by experimenting on normal animals. For example, Levaditi and MacIntosh<sup>25</sup> have found that the normal calfat, or Java sparrow (*Padda oryzivora*), can bear the subcutaneous injection of 5 mg. of atoxyl, while 2 mg. is all the infected bird can safely withstand.

*Atoxyl in Vitro.*—The action of atoxyl on *Sp. gallinarum* has been studied *in vitro*. Levaditi and MacIntosh<sup>25</sup> suspended the spirilla in a solution of atoxyl stronger than that necessary to cure the calfat and studied the effect at room temperature and at 38 C. No marked difference was observed between the spirilla in the atoxyl solution and those suspended in isotonic salt solution. At room temperature the parasites preserved their motility for several hours. Still more striking are the results of Uhlenhuth and Gross,<sup>24</sup> who studied the effect of atoxyl on the parasites at a lower temperature. These investigators mixed 1 c.c. of blood rich in spirals with 1 c.c. of a 1 per cent. solution of atoxyl and placed the mixture in the ice-chest. In this mixture the virulence of the organisms was retained for six days and motile spirilla were observed as late as the eighth day.

*Atoxyl in Vivo.*—In an attempt to determine the action of atoxyl *in vivo*, Levaditi and MacIntosh injected subcutaneously and intraperitoneally into fowls and calfats a solution of atoxyl containing the spirilla in suspension and studied the effect of the medicament on these

24. Uhlenhuth and Gross: Untersuchungen über die Wirkung des Atoxyls auf die Spirillose der Hühner. Arb. a. d. k. Gsndts-amte., 1907, xxvii, 231.

25. Levaditi (C.) and McIntosh (J.): L'Influence de l'atoxyl sur la spirillose provoquée par le *Spirillum gallinarum*. Compt. rend. Soc. de biol., 1907, lxii, 1090.

organisms by withdrawing a little of the fluid from time to time and examining it. The results were similar in the fowls and in the calfats. For a time the spirilla retained their motility, but after several hours this was lost and they agglutinated. In the controls, which received the spirilla suspended in salt solution, the parasites never lost their motility.

*No Fixation by Atoxyl.*—That atoxyl is not fixed by *Sp. gallinarum* has been shown by Levaditi and MacIntosh. Ten drops of blood rich in spirilla were mixed with fifty drops of a 2 per cent. solution of atoxyl. After two hours' contact the spirilla were freed from the atoxyl by washing and centrifugation and then injected into normal calfats. These animals became infected, as did the controls.

*The Influence of the Host.*—In the treatment by atoxyl of an infection with *Sp. gallinarum*, the species of the animal infected may play an important part. Levaditi and MacIntosh have shown that when the mouse is inoculated intraperitoneally with these spirilla it takes the spirillosis in a fairly accentuated manner, but the infection is of short duration and not transmissible in series. Against this infection in the mouse atoxyl seems to be without effect. Even when the medicament is mixed with the virus before it is injected into the mouse, the infection is not prevented and runs a course that is indistinguishable from that in the controls.

*How Atoxyl Acts.*—From these experiments Levaditi and MacIntosh conclude that atoxyl acts only by the intermediation of the animal organism. They believe that this medicament modifies the host in such a way that the means normally employed to rid it of the spirilla are exaggerated. In this way the infection is rendered light, almost imperceptible, and the crisis is called forth earlier than the one that normally puts an end to the infection. The appearance of this critical process is determined by atoxyl, even in those animals, like the calfats, in which it seems never to occur in nature. Unless treated, these birds regularly die of the infection. That these animals have a veritable crisis following the injection of atoxyl is indicated by the fact that they become refractory and elaborate antibodies which may be detected by experiments *in vitro*, for example, the immobilizing action of the serum.<sup>25</sup>

#### AFRICAN TICK FEVER.

African tick fever (*Spirillum duttoni*) is the next spirillosis to be considered. In the treatment of the experimental infection with the organisms of this disease, Vassal's<sup>26</sup> best results have been obtained with the benzidine dyes, or colors. The red colors were superior to the blues, the most efficient medicaments being trypan-red and alpha (naphtyla-

min disulphonic acid 2736 plus benzidin; see Table 2) of Nicolle and Mesnil.

*Sp. Duttoni in Untreated Mice.*—In Vassal's untreated mice the spirilla generally appeared in the blood of the animals in less than twenty-four hours after an intraperitoneal inoculation of the virus. The organisms increased rapidly during the next two or three days until they became more numerous than the red blood corpuscles. They then began to decrease and on the sixth to the seventh day suddenly disappeared. The first relapse occurred, as a rule, a day or two later, the spirilla reappearing in the blood to remain one, two or three days.

*Trypan-Red and Alpha.*—According to Vassal,<sup>26</sup> both trypan-red and "alpha" exert a protective and a curative action on this spirillosis in mice. If either is injected subcutaneously in the therapeutic dose, simultaneously with the intraperitoneal injection of the virus, the appearance of the spirilla in the blood is sometimes completely prevented, sometimes delayed until the time of the first relapse. If, on the other hand, the colors are administered twenty-four to forty-eight hours after the inoculation of the virus, at a time, therefore, when the spirilla are more or less numerous in the blood, the organisms disappear within twenty-four hours, while in the controls they are still swarming.

*Malachite Green.*—In the treatment of mice infected with the spirilla of African tick fever, Vassal<sup>26</sup> found that malachite green did not have an appreciable influence.

*Atoxyl.*—However useful atoxyl may be in the treatment of certain spirillooses, animal experiments indicate that it has little or no activity against the organisms of African tick fever. In 1906, according to Vassal,<sup>26</sup> Levaditi used atoxyl to free the tick-fever virus of a trypanosome that accompanied it, and somewhat later the former investigator,<sup>26</sup> working with the same virus, found that atoxyl was without influence on the course of the infection in mice.

*Atoxyl in the Treatment of Man.*—In the treatment by atoxyl of tick fever in man, a similar failure is reported by Breinl and Kinghorn.<sup>27</sup> Two cases of this disease were studied at the Liverpool School of Tropical Medicine. From the very first day both patients were given injections of a 20 per cent. solution of atoxyl. The injections were made daily for two weeks, beginning with 0.6 c.c. and increasing to 1 c.c. In spite of this, no influence was observed either on the parasites or on the course of the infection.

26. Vassal (J. J.): Action des couleurs de benzidine sur le spirille de la "tick fever" (*Sp. duttoni*). Compt. rend. Soc. de biol., 1907, lxii, 414.

27. Breinl (A.) and Kinghorn (A.): Ueber die Wirkung des Atoxyl bei afrikanischem Rückfallfieber. Deutsch. med. Wochenschr., 1907, xxxiii, 299.



## EUROPEAN RELAPSING FEVER

The third spirillosis that we are to take up is European relapsing fever, the etiological agent of which is the long known *Spirillum obermeieri*. According to the work of Glaubermann,<sup>28</sup> atoxyl, when administered in large doses, seems to have a favorable effect on this infection. In the course of a violent epidemic of the fever that raged in Moscow in the spring of 1907, this investigator treated seventy patients. In each instance the true nature of the disease was determined by the finding of the organisms in the blood, and in the undoubted cases only those patients were chosen for treatment who were shown by their histories to be having the first attack. In order to have comparable results, in no case was the atoxyl treatment instituted until the day after the fall of temperature at the end of the first attack. The treatment was given daily. The first thirty patients received comparatively small doses, varying between 0.6 and 1.7 gm. in the course of six to eleven days. These patients were manifestly less well influenced than forty others that received 1.8 to 4.6 gm. of the medicament in seven to fourteen days. The maximum dose given was 0.5 gm. In the treated patients the interval between the first attack and the first relapse was apparently not altered by the atoxyl, but where a relapse occurred the duration of this was shortened by about forty hours, and in a number of cases the relapse seemed to have been prevented. For example, in untreated patients Glaubermann observed a first relapse in 87 per cent. of the cases, whereas in the forty patients last treated it occurred in 32 per cent.

## SYPHILIS

*Atoxyl and Syphilis.*—Since the discovery that atoxyl is active against syphilis, a large literature<sup>29</sup> has arisen on the use of this drug in the experimental and naturally acquired form of this disease. The results of animal experimentation will be given before the treatment of man is taken up.

*Experimental Prophylaxis.*—The prophylactic action of atoxyl in animals is easily shown. Rabbits<sup>30</sup> inoculated with syphilitic virus and

28. Glaubermann (J.): Klinische Beobachtungen über die Einwirkung des Atoxyls auf den Verlauf des Rückfallfiebers. Berl. klin. Wehnsehr., 1907, iii, 1143.

29. A review of the literature upon the use of atoxyl in syphilis may be found in Paul Salmon's article entitled: L'Arsenie dans la syphilis. Am. de l'Inst. Pasteur, 1908, xxii, 66.

30. Uhlenhuth (P.), Hoffman (E.) and Weidanz (O.): Ueber die präventive Wirkung des Atoxyl bei experimenteller Affen- und Kaninchen-Syphilis. Deutsch. med. Wehnsehr., 1907, xxxiii, 1590.

then treated regularly with atoxyl showed neither a specific iritis nor nodules on the iris, contrary to what occurred in the controls. Monkeys<sup>31</sup> have also been protected by injections of this medicament. Of eight inoculated with syphilitic virus and treated at once with atoxyl, not one took the infection.

*Abortive Action.*—The power of atoxyl to abort syphilis is not limited to cases treated immediately after the infection. In one experiment of Metchnikoff's<sup>32</sup> two monkeys were inoculated with syphilitic virus, and in neither case was treatment instituted until fifteen days later, when each received a single injection of atoxyl (33 mg. pro kilo). No further treatment was given, yet neither of the monkeys contracted syphilis. The control showed the disease on the thirty-fourth day.

In searching for the interval during which atoxyl might act preventively, Metchnikoff,<sup>32</sup> in one case, waited until the very beginning of the primary lesion before treating the monkey. Ten centigrams of atoxyl sufficed to stop at once the development of the lesion. In this case, however, the single injection did not abort the disease; the animal was not cured and a relapse soon occurred.

From this, according to Salmon,<sup>33</sup> it would seem that, before the appearance of the primary, atoxyl may be used prophylactically, but when this lesion is visible it is too late to abort the disease. According to this investigator, at the moment the initial lesion appears the infection seems to become definitely chronic and the necessary doses of atoxyl must be repeated for a long time to effect a cure.

*Immunity.*—No immunity against syphilis is acquired when the development of the disease has been prevented by atoxyl. For example, two monkeys,<sup>32</sup> previously protected from infection by atoxyl, were inoculated a second time with syphilitic virus, seventy-seven and ninety-one days, respectively, after the first inoculation. Both contracted characteristic primary lesions.

*Experimental Cures.*—In monkeys lower than the anthropoid ape, the initial lesion, attenuated syphilis, may be cured, according to Salmon,<sup>33</sup> after a single injection of atoxyl. The lesion already appears modified after twenty-four hours, and at times in less than four days has almost completely disappeared.

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31. Uhlenhuth (P.) Hoffman (E.) and Roscher (K.): Untersuchungen über die Wirkung des Atoxyls auf die Syphilis. Deutsch. med. Wchnschr., 1907, xxxiii, 873.

32. Metchnikoff (E.): Sur la prophylaxie de la syphilis. Ann. de l'Inst. Pasteur, 1907, xxi, 753.

33. Salmon (P.): L'Arsenic dans la syphilis. Ann. de l'Inst. Pasteur, 1908, xxii, 66.

*Relapses in Experimental Syphilis.*—A single injection of atoxyl, however, is not always sufficient to cure even the lower monkeys. The primary lesion may disappear under the influence of the drug, but if the treatment is not repeated one may subsequently find at the site of the old lesion scales, or crusts, or an infiltration of the skin, testifying to a recrudescence in the activity of the parasites.<sup>33</sup>

*Efficiency of Atoxyl.*—As an indication of the efficiency of an energetic treatment by atoxyl we may refer to the fact that the inoculation of the organs (spleen and bone-marrow) of animals previously treated by atoxyl only rarely infects susceptible animals,<sup>34</sup> while the inoculation of the organs of untreated animals nearly always does.

*Prophylaxis in Man.*—Metchnikoff<sup>32</sup> reports the cases of two men who feared they had contracted syphilis and who begged to be inoculated prophylactically with atoxyl. Each of these received two injections of 0.5 gm. of atoxyl, and neither contracted the disease. Nevertheless, as it was impossible to be certain that the men treated had really been inoculated with syphilis, Metchnikoff declined to draw any conclusions from these cases.

*Curative in Man.*—Clinically the action of arsenic is comparable to that of mercury (Salmon<sup>33</sup>). It cures the lesions that mercury cures (Salmon<sup>33</sup>). It is the third specific (Hallopeau<sup>35</sup>). Toward it all of the syphilides react in the same way (Salmon<sup>33</sup>). The chancre heals rapidly (Salmon<sup>33</sup>). Exanthemata disappear, papules flatten, annular syphilides dry, ulcers heal, and gummata yield to its influence (Lassar<sup>36</sup>).

To cure the lesions of syphilis the drug must be properly given. If the dose is too small, it is without effect; if too large and given repeatedly, permanent blindness or intense intoxication, or both, may result. According to Salmon, the correct dose of atoxyl for man is 0.5 gm. He regards this dose as non-toxic, therapeutically necessary and sufficient, and states that it constitutes a maximum which it is useless and at times dangerous to surpass.<sup>33</sup>

This investigator uses weak solutions of the medicament, 10 to 15 per cent., and sterilizes these at 100 C. for two minutes. As aqueous solutions of atoxyl do not keep, it is best to prepare them only a short time before using. The injections may be made subcutaneously or intramuscularly.

34. Neisser (A.): Atoxyl bei Syphilis und Framboesie. Deutsch. med. Wehnschr., 1907, xxxiii, 1521.

35. Hallopeau (H.): Sur un danger de la médication par l'atoxyl et l'obligation qu'il impose. Bull. Acad. de méd., 1907, lviii, 61.

36. Lassar (O.): Atoxyl bei Syphilis. Berl. klin. Wehnschr., 1907, xlv, 684.

Given in this way, atoxyl usually acts rapidly on the syphilitic lesions and seems to be without danger for the patients. In treating 181 patients, into whom Salmon<sup>33</sup> made 1,349 injections of the drug, not one had ocular trouble. It is true that larger doses, up to 1 gm. and more, have been given without inconvenience, but the experience of Koch, who has tried the drug on a large scale in Africa in the treatment of sleeping sickness, teaches that 0.5 gm. is the safe dose.

*Where Atoxyl Is Indicated.*—The advocates of mercury and potassium iodid may question the need or value of atoxyl in the treatment of the average case of syphilis, but even they should admit that for some patients and for some lesions atoxyl is clearly indicated. Where patients manifest an idiosyncrasy toward mercury or potassium iodid and can not take these medicaments, atoxyl should certainly be tried. It should also be tested on those lesions and forms of syphilis which heal slowly or are refractory to mercury. It is perhaps in the treatment of such patients and lesions that the effect of the atoxyl treatment has been most brilliant.

*Duration of Treatment.*—How long the atoxyl injection will have to be continued before the disease can be considered cured can not yet be stated. The continued observation of many cases alone will decide this. From the well-known chronicity of the disease, however, it is evident that we must expect relapses if the treatment is stopped too soon. Even when the lesions appear healed and when large doses of atoxyl have been given, relapses are apt to occur if the treatment is interrupted. In one case a chancre that measured 3 c.c. was apparently healed after five injections of 0.75 gm. each. The treatment was stopped, and twenty days later the chancre opened again (Salmon<sup>33</sup>).

*Idiosyncrasy.*—Although atoxyl has shown its efficiency in many cases of syphilis, it can not be used in all. We must recognize that a certain proportion of people can not bear this drug well. The percentage of these among men is about 12, among women it is still higher.<sup>33</sup> The symptoms of intoxication—colic, nausea, vomiting, etc.—appear about ten hours after the injection of the drug, sometimes after the first injection, but more frequently after the fourth.<sup>33</sup> These symptoms rarely last longer than four hours, are more alarming than serious and are allayed by opium (Salmon<sup>29</sup>).

*Limited Applicability of Atoxyl.*—Atoxyl is not applicable in all cases. As we have seen, some patients can not take this drug. It is obvious that for these some other treatment must be employed. In addition to these cases, there are a few syphilitic lesions that are influenced slowly or not at all by atoxyl. For these we should use either a totally

different treatment or else associate some other medicament with atoxyl, alternating or giving them simultaneously.

*Alternative Treatment.*—The injection of atoxyl may be alternated with that of mercury. From the work of Ehrlich on trypanosomes it would seem that by thus energetically attacking the organism of syphilis from two sides in quick succession the destruction of the parasites may be brought about more quickly and the production of strains resistant to either of the medicaments may be prevented. In practice Salmon<sup>33</sup> has found that this method is very effective against lesions that have grown torpid or refractory when treated by either atoxyl or mercury alone.

*Simultaneous Treatment with Two Medicaments.*—The simultaneous administration of atoxyl and mercury is the last treatment of syphilis we will mention. Salmon<sup>33</sup> reports having combined with his atoxyl injections the most varied mercurial treatments. It is gratifying to note that this double treatment with atoxyl and mercury has been given in the majority of the cases without inconvenience, but on the real value of this method the future alone will enable us to place a proper estimate. All that can be said at present is, that by this procedure already, according to Salmon,<sup>33</sup> remarkable results have been obtained.

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# THE AGGLUTINATING POWER OF THE BLOOD SERUM OF TUBERCULOUS PATIENTS

SERUM DIAGNOSIS—SERUM PROGNOSIS \*

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The serum diagnosis of tuberculosis is to-day one of the most generally employed and most reliable laboratory methods of diagnosis.

## 1.—HISTORICAL

It is well known that the ordinary cultures of the bacillus of Koch can not be used for agglutination. Arloing, however, in 1898,<sup>1</sup> obtained a fluid homogeneous culture of the tubercle bacillus and demonstrated its specific agglutinability by the serum of tuberculous human beings or animals, thus rendering possible the serum diagnosis of tuberculosis. Arloing and Paul Courmont<sup>2</sup> later perfected the method, determining the best manner of producing homogeneous cultures, applying the serum diagnosis to hundreds of patients and studying in these and on animals which had been rendered tuberculous the agglutinating power of the blood. Paul Courmont has further studied<sup>3</sup> local serum diagnosis (diagnosis of the nature of pathological serous fluids by their agglutinating power) and the serum prognosis of pleurisies. To-day the Lyonese

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1. Arloing (S.): Sur l'obtention des cultures homogènes du bacille de la tuberculose, *Compt. rend. Acad. d. sc., Paris*, May 19, 1908; Agglutination des bacilles de Koch par le sérum sanguin des tuberculeux, *Cong. franc. de méd., Montpellier*, April 13, 1898; *Acad. d. sc., Paris*, May 16, 1898.

2. Arloing (S.) and Courmont (Paul): De l'obtention des cultures homogènes les plus propices à l'étude du phénomène de l'agglutination par le sérum sanguin des tuberculeux, *Compt. rend. Acad. d. sc., Paris*, Aug. 8, 1898; Recherche et valeur clinique de l'agglutination du bacille de Koch. *Compt. rend. de l'Acad. d. sc., Paris*, Sept. 19, 1898; *Cong. de la tuberc., Paris*, 1898; Séro-diagnostic de la tuberculose, *Cong. de la tuberc., Berlin*, 1899; *Ztschr. f. Tuberk.* 1900, i, No. 1; *Gaz. d. hôp., Paris*, Dec. 1, 1900.

3. Courmont, Paul: Séro-diagnostic des épanchements tuberculeux, *Cong. de la tuberc., Paris*, 1898; *Compt. rend. Soc. de biol.*, 1898; L'agglutination du bacille de Koch par les épanchements tuberculeux; *Arch. de méd., expér.*, November, 1900.

method is employed in all parts of the world and numerous observations have been made on this question.<sup>4</sup>

Among the students who have confirmed this work may be mentioned: In France: Widal and Ravaut, Dieulafoy, Schrapf, Sabareanu and Salomon, pupils of Professor Landouzy, in Paris; Ferre, Mongour and Buard, in Bordeaux; Carrière, in Lille; Hawthorn, in Marseilles; Lagriffoul, in Montpellier; Bard and Humbert, in Geneva, Switzerland; Bendix, Rumpf and Guinard, Romberg, in Germany; Kazarinow, Shakerin, in Russia; Marzagalli, Caffareno, Marchetti and Stefanelli, Marini, in Italy; Thomescu and Gacesky, in Roumania, etc.

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4. Arloing, S., Bayle and Dumarest: Etude sur les rapports entre la séro-agglutination et l'évolution de la tuberculose chez l'homme, Cong. de la tuberc., Paris, 1905.

Arloing, S., and Courmont, Paul: Variations de l'agglutinabilité des bacilles de la tuberculose: deux mémoires, Rev. de la tuberc., 1904.

Bronstein: Soc. de pédiat. de Moscou, Vrach, 1901.

Courmont, Paul: Valeur sémiologique de la réaction agglutinante chez les tuberculeux, Cong. de Lyons de l'Assn., franç. pour l'avancement d. sc., 1906; Tuberculose latente et séro-diagnostic, Bull. Soc. med. d. hôp. de Lyons, 1904.

Dieulafoy. Semaine méd., 1903; Clin. méd. de l'Hôtel-Dieu de Paris.

Froment: Séro-diagnostic de la tuberculose chez le vieillard, Compt. rend. Soc. de biol., 1903.

Hawthorn: Séro-réaction tuberculeuse. Compt. rend. Soc. de biol., June 6, 1902; Jour. de physiol. et path. gén., 1903, No. 1.

Humbert: Diagnostie de la granulie par la séro-réaction. Rev. de la tuberc., 1904, No. 4.

Il Vento: Sull' agglutinabilità del bacille tuberculare e sua importanza diagnostica, Riforma med., 1902, 266.

Kazarinov: Contribution a l'étude de séro-diagnostie tuberculeux, Nevrologicheski, 1901, 849.

Lagriffoul and Verges: Compt. rend. Soc. de biol., 1903.

Landis: Studies in agglutination in tuberculosis, Jour. Med. Research, 1903.

Marchetti and Stefanelli: Sulla séro-reazione tuberculose. Riv. crit. di med. clin., 1903.

Marzagalli and Caffareno: Sur l'agglutination du bacille tuberculeux. XII Cong. Soc. ital. de méd. int., Rome, October, 1902.

Mongour and Buard: Compt. rend. Soc. de biol., 1899.

Neisser, J.: Valeur pronostique de la séro-réaction, Cong. ital. di med. int., Genoa, 1905, 920.

Ravenel and Landis: Agglutination studies in tuberculosis, Med. News, 1907.

Rodet and Lagriffoul: La séro-réaction tuberculeuse. Jour. de physiol. et path. gén., 1902.

Rumpf and Guinard: Recherches sur la séro-réaction tuberculeuse, Presse méd., 1902, No. 24; Deutsch. med. Wchneschr., 1902, No. 8.

Schrapf: Diagnostie de la tuberculose par la séro-agglutination. Arch. de méd. mil., February, 1902.

Widal and Ravant: Agglutination du bacille de Koch dans 24 cas de pleurésies tuberculeuses, Cong. de la tuberc., London, 1901.

If, on the contrary, some authors have contested the importance and value of serodiagnosis, their attitude, I and my associates believe, arises from their not having avoided the following causes of error.

## 2.—CAUSES OF ERROR

### I. TECHNIC

First, one must possess a good agglutinable bacillus. We have shown that agglutinability is a property not common to all bacilli of Koch. Our bacillus A (human tuberculosis, Arloing) fulfils the conditions of facility of culture and agglutinability. This organism we have sent to all who have sought cultures, and most of the results obtained in different parts of the world depend on investigations made with this bacillus. The liquid homogeneous culture must be developed and employed under the conditions which we have explained at length elsewhere. The cultures, which should be four to eight weeks old, must be diluted with a 0.7 per cent. salt solution and tested with the standard serum, and mixed with the serum to be tested in suitable proportion; it is necessary to take into account only those reactions visible to the naked eye. These steps are easy to follow in a well-appointed laboratory; we can, moreover, furnish tubes of homogeneous cultures ready to be employed, just as one provides tuberculin, dry or liquid, for tuberculin reactions.

But it is evident that technical modifications in the preparation of the cultures, in their age, their dilution, etc., modify their agglutinability so that it becomes impossible to compare the results obtained with these cultures with those obtained by ourselves and by those who have strictly followed our instructions.

### II. APPRECIATION AND VALUE OF THE DEGREE OF AGGLUTINATION

It is advised that in the case of an adult the serum and the culture be mixed in three small test-tubes in the following proportions: (1) one part of serum to five of culture; (2) one to ten; (3) one to fifteen. Under these conditions the serum of a man free from all evident or latent tuberculosis should not agglutinate ordinarily at 1 to 5, whereas the serum of the tuberculous will agglutinate in dilutions varying between 1 to 5 and 1 to 15 or 20, and rarely in higher dilutions.

If, however, one change the conditions the results are materially different. For instance, if one should employ cultures which were not agglutinable, the results would be wholly negative. If, on the contrary, one employs cultures which are too agglutinable, one obtains, with a given serum, much higher degrees of agglutination than are obtainable with cultures prepared strictly according to the above directions, and



such results can no longer be compared with ours. This, for example, is what happened in the observations of Kinghorn, who obtained agglutinations at much higher dilutions than we did. It is well known that every normal serum possesses a certain normal agglutinating power; the specificity of the agglutinating reactions is, therefore, relative, quantitative and not qualitative. It is only within certain limits that the agglutinating reaction with a given bacillus has a specific and diagnostic importance, and these limits vary according to the different animal species. For instance, the serum of a healthy dog agglutinates our homogeneous culture at a dilution of 1 to 30; the serum of an adult non-tuberculous cow agglutinates it ordinarily at 1 to 5. Moreover, the agglutinability of the serum of a given animal species varies in degree according to age. Arloing has shown that the serum of the calf does not agglutinate at 1 to 5, whereas the serum of a healthy cow does agglutinate at this dilution. Consequently, for a given animal species, the agglutination of a bacillus is specific only when it is above the ordinary degree of agglutination of the normal serum of this species for this bacillus. Moreover, the age must likewise be taken into consideration. To summarize: A serum agglutination has diagnostic value for a given subject only when it surpasses the agglutinating power of the serum of normal subjects of the same species and the same age.

For human beings it is not easy to fix this limit. It is always difficult to prove that the subject is healthy and has not a latent tuberculous lesion. Nevertheless, for an adult subject, under the exact conditions of our technique, the limit of pathological agglutination seems to begin at a dilution of 1 to 5. We shall see, further on, that this limit is lower in children. But it is evident that if one employs cultures which are much more agglutinable than ours, this limit will be raised above 1 to 5, because under these conditions the normal agglutinating power of the serum of healthy subjects would surpass this limit. One must, then, consider as specific only such serum reactions as are much more intense. It is certainly through their not having taken these considerations into account that some authors, and especially Kinghorn, have considered as specific certain serum reactions due to the normal agglutinating power and have found as many positive reactions in healthy people as in those who are tuberculous. Kinghorn finds, in fact, many reactions at dilutions of 1 to 75 and 1 to 100, degrees of agglutinability which have hardly ever obtained in a tuberculous man. His cultures, therefore, must be regarded as much more agglutinable than ours, so that the nor-

mal human serum, which for us agglutinates only at dilutions below 1 to 5, agglutinates for Kinghorn much more readily. such agglutinations being considered by him as specific reactions.

### III. CLINICAL INTERPRETATION.

One must take care not to regard the serum reaction as an infallible sign, promising a diagnosis with mathematical precision. Like every pathological sign, like the ocular reaction or like that following the injection of tuberculin, this reaction must be interpreted and discussed in comparison with the other symptoms furnished by the study of the case. The serum diagnosis is valuable only in cases in which a clinical examination has already been made, "in the case of a suspected subject," as we have already insisted with Arloing as long ago as 1898. Applied to healthy subjects not suspected of tuberculosis it has of itself but slight value.

One must remember also that general serum diagnosis (with blood serum) does not point out the localization of the lesions, but only the existence of tuberculosis; it is for the clinician to apply to a local lesion the results of his serum diagnosis. We repeat that all these directions apply not only to serum diagnosis, but to all methods based on the employment of tuberculin (subcutaneous injection, ocular reaction) which are, moreover, open to many other objections.

#### 3.—PROOF OF THE VALUE OF SERUM DIAGNOSIS

The best proofs of the value of this method are the good practical results which serum diagnosis has given to a great number of authors, but there are two kinds of proofs which are especially conclusive.

1. *Bovine Statistics*.—In cows statistics may be obtained in which the serum reaction is controlled by autopsy. Under these conditions Arloing has determined that serum diagnosis is always negative when a cow is non-tuberculous and positive in 98 per cent. of cases in which there are tuberculous lesions.<sup>5</sup>

2. *Statistics with Pleurisy in Man*.—In pleurisies in the human being one can obtain evidence as to the tuberculous or non-tuberculous nature of the malady by the consideration of clinical observations, together with inoculations and cytology. In such conditions, in statistics of 112 cases, we have never had a positive reaction with the pleural fluid when, by all other criteria, the pleurisy was non-tuberculous; on the contrary, we have had 76 per cent. of positive reactions in cases in which the pleurisy was

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5. Arloing (S.): Séro-diagnostic de la tuberculose chez les bovides. Jour. de méd. vét. de Lyon, September, 1900.

regarded as tuberculous.<sup>3</sup> If the results of agglutination with the blood serum of human beings (tuberculous or not) are apparently less easy to interpret, this depends on the variations of the agglutinating power according to the nature, the gravity, the stage of healing or curability of the lesions, as well as according to the age of the subject. These considerations may be summarized as follows:

#### 4.—THE AGGLUTINATIVE REACTION IN PRACTICE. SERUM DIAGNOSIS

According to our own personal statistics (Arloing and Courmont), covering more than 1,200 cases, we have obtained positive serum reactions: I, in tuberculous patients (90 per cent.); II, in hospital cases, apparently non-tuberculous (40 per cent.); III, in apparently healthy subjects (30 per cent.).

##### I. TUBERCULOUS PATIENTS

The agglutination here varies in frequency and in intensity, according to the following conditions:

*The Localization of the Lesions.*—The serum of patients with localized tuberculosis (so-called "surgical" cases) is often less agglutinating (75 per cent. in cases of tuberculosis of bone, of skin, of lupus<sup>6</sup>). The serum of patients with tuberculosis of viscera, lung, pleura and other serous membranes, as well as intestine, agglutinates in a higher degree.

2. *The Gravity of the Lesions.*—The most serious cases of tuberculosis, those with widespread lesions, rapid consumption (consumptive subjects attacked by tuberculous pneumonia, meningitis, acute miliary tuberculosis), nearly all give negative serum reactions. On the other hand, the serum of curable patients, such as those with fibroid tuberculosis, gives the largest proportion of positive reactions (pleurisy *a frigore*, fibroid pulmonary tuberculosis, chronic bronchitis or emphysema with slight tuberculous lesions, curable adenitis, etc.). Similar conditions are observed with animals which have been rendered tuberculous experimentally. Two conclusions may be drawn from these observations: From the point of view of diagnosis, the method will not give such good results in the grave and rapid forms of the disease, but it will reveal latent cases which advance slowly and in which cures are possible; that is, those cases in which the diagnosis is both most difficult and most useful. As to serum prognosis, I shall speak later.

6. Courmont, (Paul): Le séro-diagnostic des tuberculoses dites chirurgicales, Thèse de Clément, Lyons, 1900.

7. Courmont, (Paul), and Nicolas: Séro-diagnostic tuberculeux chez les lupiques, Soc. méd. d. hôp. de Lyon, 1907.

3. *Healed Lesions.*—The serum of tuberculous patients who are convalescent agglutinates very well. One must realize that the agglutinating power of the blood persists long after the anatomical cure of the lesions, and thus it comes to pass that serum agglutination may allow a retrospective diagnosis in cases of cured tuberculosis (for instance, in a past adenitis or pleurisy).

On the other hand, one must always remember the possibility of such a condition when one attempts to interpret the serum reaction in a subject who has clinically no sign of tuberculosis. The reaction here might be due to a persistent power of agglutination remaining in the blood after the cure of an old tuberculosis which has healed without leaving any trace. This difficulty, moreover, is not inherent in serum diagnosis alone; we have seen positive ocular reactions in old subjects, whereas the autopsy and inoculation of the organs showed no trace of tuberculosis in evolution or the presence of any bacilli of Koch. This merely shows that laboratory procedures of diagnosis must be considered in each particular case in their relation to the clinical observation.

4. *Age.*—The serum of the newly born does not agglutinate (Romberg, Descos<sup>8</sup>); that of tuberculous children agglutinates, but less than that of adults. The degree of agglutinating power rises with the age of the children. It appears, therefore, that the serum reaction has a positive significance in children at a lower degree of agglutination than in adults; this is very important, because of its practical application.<sup>9</sup> It is in adults that the serum reaction presents the maximum of frequency and intensity.

In the aged<sup>9</sup> one finds many weak serum reactions caused by old tuberculous lesions, more or less healed, but strong serum reactions are important in revealing old tuberculosis not yet completely extinct. It is very important to appreciate these variations according to age, for practical application; that is, for the theoretical question of latent tuberculosis. The same degree of agglutination has not the same importance at different ages. On the other hand, the results of serum diagnosis at different ages agree absolutely with those of the necropsy statistics of Naegeli in Germany.

## II. REACTIONS IN HOSPITAL CASES APPARENTLY NOT TUBERCULOUS

Here the serum reaction is positive in from 35 to 40 per cent. of the cases; this is not astonishing when one considers the great frequency of

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8. Descos: La séro-diagnostic de la tuberculose chez les enfants, Thèse, Lyon, 1902; Jour. de physiol. et path. gén., 1903, No. 1.

9. Descos: Le séro-diagnostic de la tuberculose chez le vieillard. Bull. Soc. méd. d. hôp. de Lyons, March 22, 1904.

more or less latent tuberculosis in hospital patients. With tuberculin one arrives at analogous results. Beck, in Berlin, observed 46 per cent. of positive tuberculin reactions in 2,000 patients who were apparently non-tuberculous.

Acute infections do not, as a rule, confer on the serum an agglutinating power for the bacillus of Koch. One must, however, classify typhoid fever separately, for 75 per cent. of typhoid patients agglutinate tubercle bacilli just as if they were tuberculous, whereas autopsy may show no tuberculous lesions. But from a theoretical point of view my experiments, with Arloing, in men and animals, show that there is no relation between the agglutinating power of serum on typhoid bacilli and tubercle bacilli. It is not apparently the same agglutinin which acts on the two bacilli, but two distinct agglutinins. The cause of this double agglutinating power of the typhoid serum is still obscure. It is, perhaps, due to an accidental invasion of Koch's bacilli through the intestinal ulcerations, or to a sort of displacement of tubercle bacilli retained in the organism. At all events, it destroys the value of the application of the tuberculosis serum reaction for the distinction between typhoid fever and tuberculosis.

Serum diagnosis of tuberculosis is less valuable in the acute forms than in the torpid and chronic forms of the disease. The same inconvenience exists with the tuberculin reaction, which can not be applied to febrile cases, and with the ocular reaction, which is positive in most cases of typhoid fever without the coexistence of tuberculosis.<sup>10</sup>

#### REACTION IN APPARENTLY HEALTHY SUBJECTS

The serum reaction is positive in about 30 per cent. of apparently healthy individuals. It also reveals latent tuberculosis, no matter how slight this may be, but, as many cases of latent and slight tuberculosis are compatible with very good health, the serum reaction in such instances has only the value of a *réaction d'attente* (expectant reaction), and without other symptoms the serum reaction has no practical importance—for instance, in soldiers. We may observe, furthermore, that the results of tests with tuberculin, in healthy subjects, confirm those of the serum diagnosis (see the statistics of Beck).

#### 5.—COMPARISON OF SERUM DIAGNOSIS AND TUBERCULIN REACTIONS. ADVANTAGES OF THE SERUM REACTION

If one compares the results given by serum diagnosis and tuberculin reactions (subcutaneous injection or ocular reaction), one sees that these methods give similar results: the serum diagnosis, however, has many

10. Arloing (F.): Ophthalmo-réaction, Jour. de physiol. et path. gén., 1908.

advantages. With all three methods the results are positive in most cases of active tuberculosis; the cases in which no reactions are obtained are often the gravest instances; for example, advanced consumption. With all three methods the results are positive in a fairly large number of cases in which neither the clinical examination nor even, sometimes, the autopsy reveals tuberculosis. The accordance of the results suggests that here there is latent tuberculosis, with very slight lesions, such as are often compatible with good health, lesions which are only revealed by this very delicate laboratory method. It is very remarkable that injections of tuberculin and serum diagnosis give about the same percentage of positive reactions in patients who are evidently non-tuberculous (40 per cent. with the serum diagnosis and 16 per cent. with the tuberculin, according to Beck). It is also curious to see that the ocular reaction is positive in typhoid cases, just as is the serum reaction. At all events, the few objections which one can make to the serum diagnosis (causes of error in feverish cases and in typhoid fever, the great sensitiveness of the method which reveals the slightest tuberculous infections, even those compatible with health) are equally applicable to the injection of tuberculin and the ocular reaction, as we have explained above.

The special advantages of serum diagnosis are the following:

1. *Absolute Harmlessness*.—The taking of a little blood can not give rise to the sometimes serious accidents or inconveniences ascribed, and with reason, to the ocular and other tuberculin reactions.

2. *Facility of Application*.—A few drops of blood suffice, while it is unnecessary to keep the patients under observation for several days, as in the two other methods.

3. *Importance of the Variations of the Agglutinating Power*.—Because of the harmlessness and facility of application of the method, one may repeat the reaction as often as he will, and the variations of the agglutinating power are of great importance, not only for diagnosis, but also for prognosis (see further).

4. *The Possibility of Local Serum Diagnosis*.—This facility does not exist with other methods.

#### 6.—LOCAL SERUM DIAGNOSIS

The serum reaction is ordinarily made with blood serum, in which case it only affords a general serum diagnosis, simply revealing the general specific impregnation of the blood with the products of a given infection, no matter what the lesions may be. But, in our work at Lyons, we established, as long ago as 1898, the possibility and usefulness of local serum diagnosis.<sup>3</sup> This is made with local serous effusions, for

instance, in pleurisy. We have pointed out that when a serous membrane is infected by tuberculosis a local reaction is produced and agglutinins are formed locally, independently of what happens in the blood. The search for a serum reaction with pleural fluid furnishes the proof of the existence of local tuberculosis. Our various observations on the subject (more than 200 cases of effusion, of which 115 were tuberculous pleurisy) have been confirmed by Mougour and Buard, Widal and Ravaut, Dieulafoy, Landouzy, Sabareanu and Salomon, Hawthorn in France, Bendix in Germany, Kazarinow in Russia, Marini, Marchetti and Stefanelli in Italy,<sup>4</sup> and other authors whose statistics are similar to ours. The most conclusive results are given by pleural fluids. The fluid of tuberculous pleurisy agglutinates (at least at 1 to 5) in 76 per cent. of the cases in adults (statistics of 115 cases). Tuberculous pleurisy which give negative results are always of grave character. Non-tuberculous fluids will not agglutinate even at a dilution of 1 to 5 (with the exception of two or three doubtful cases). The agglutinating power of tuberculous fluids is ordinarily less elevated than that of the blood serum, but it may sometimes be more elevated and it may exist only in the pleuritic fluid and not in the blood. It would, therefore, seem that the pleural membrane can produce (*in loco*) agglutinative substances.

In practice: (1) Positive serum reaction at dilutions of 1 to 5 and above is a sign of great value as indicating the tuberculous nature of a pleurisy. The careful comparison of the serum diagnosis with the cytology and the results of inoculation of fluid in guinea-pigs proves the absolute accordance of the three methods. The serum diagnosis has the advantage of greater facility and rapidity; one does not have to keep the patient under observation; a few drops of liquid suffice, and this small quantity of fluid can be transported easily to the laboratory for examination.

2. A negative reaction constitutes only a presumption against the diagnosis of tuberculosis. One must, in this case, repeat the experiment.

3. A comparison of the agglutinating power of the blood with that of the pleural fluid would give interesting results. One can draw the same conclusions from tests made with other pathological fluids (especially ascites and hydarthroses), except in cases of meningitis, in which the cerebrospinal fluid is never agglutinative.

#### 7.—SERUM PROGNOSIS

The general idea of the serum prognosis in disease and the significance of the agglutinating reaction in the evolution of infectious diseases was suggested by me for the first time in 1896-7, apropos of ty-

phoid fever.<sup>11</sup> I have shown that the degree of the agglutinating power of the blood is more intense when the infection is less grave and the resistance of the subject is greater. This is probably applicable to all infectious diseases running a typical course (self-limited diseases). For tuberculosis the question is more complicated on account of the variability of the form and the duration of the illness. But it would be as important as it is difficult to establish a means of prognosis through the varying agglutinating power in tuberculous patients. Subsequently (Congress of Tuberculosis in Berlin, 1902), with Arloing, I have been able to assert that "the agglutinating power seems to be inverse to the gravity of the tuberculous infection," and in 1900 we arrived at the same conclusions in regard to animals which had been made tuberculous experimentally.<sup>12</sup> The principal arguments on which serum prognosis in tuberculosis is based are the following:

1. *General Statistics.*—The tuberculous in whom the serum is not agglutinating (10 to 15 per cent.) are nearly all very seriously ill; subjects who have advanced consumption, miliary tuberculosis, caseous pneumonia or meningitis have, nearly all, a negative serum reaction.

2. *Experiments in Animals Made Tuberculous Experimentally.*—The agglutinating power is higher when the tuberculosis is less virulent and the animal very resistant, and conversely.<sup>12</sup>

3. *Variations of Intensity of the Agglutinating Power of Tuberculosis.*—These variations appear to be dependent on the prognosis of the disease. Very elevated reactions are found especially in subjects in whom the tuberculosis is slight or in the course of healing (local tuberculosis of the viscera, fibroid tuberculosis of the lungs, primary pleural tuberculosis of Landouzy, etc.). Conversely, weak agglutinations are found especially in patients very seriously ill.

4. *Variations of the Agglutinating Power in the Same Subject.*—If one follows for a considerable period a single tuberculous subject, one sees frequently an elevation of the agglutinating power of his serum if the patient be convalescent, and, on the contrary, a reduction if the disease is progressive, while at times the reaction may even disappear completely. As examples the two following cases may be cited:

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11. Courmont (Paul): Signification de la réaction agglutinante chez les typhiques, Thèse de Lyons, 1897, Compt. rend. Soc. de biol., 1897-1898.

12. Arloing (S.) and Courmont (Paul): Des causes qui modifient le pouvoir agglutinant des sujets expérimentalement tuberculeux, Jour. de physiol. et path. gén., January, 1900, No. 1.



CASE 1.—*Tuberculous Pleurisy with Favorable Serum Prognosis.*—Giuseppe, —, aged 18; has benign sero-fibrinous pleurisy without complications, and will recover completely.

#### AGGLUTINATING POWER OF PLEURITIC FLUID

9th day .....	+ 5
14th day .....	+10
21st day .....	+15

CASE 2.—*Tuberculosis with Unfavorable Serum Prognosis.*—M., — aged 28; pregnant; double pleurisy with fever; secondary galloping consumption: death in 96 days.

#### AGGLUTINATING POWER

OF BLOOD		OF PLEURITIC FLUID	
20th day .....	+10	20th day .....	+ 5
50th day .....	+ 5	50th day .....	0
80th day .....	0	80th day .....	0
95th day .....	0	95th day .....	0

In the first case the agglutinating power, as may be observed, increased until recovery; in the second it fell and eventually disappeared, remaining absent until death.

5. *Mortality from Pleurisy According to the Agglutinating Power of the Pleural Fluids.*—We have studied more than 120 cases of tuberculous pleurisy and followed the patient during eight years. If one compares the mortality of patients in whom the pleural fluids showed an agglutinating power with that of patients whose fluid was not agglutinating one arrives at the following results: 75 per cent. of recoveries in cases with positive reaction, 73 per cent. of deaths in cases with negative reaction.

I published these statistics three years ago<sup>13</sup> at the Congress of Tuberculosis in Paris, 1905, and in *The Journal of the American Medical Association*. Ravenel arrived at analogous conclusions. Eight years ago Bendix,<sup>14</sup> in Germany, wrote also in favor of serum prognosis.

These facts offer further support to that which I have asserted with regard to typhoid fever, namely, that the agglutinating power is an index of the protective reaction of the system.

#### CONCLUSIONS

I. The agglutinating power of the humoral fluids in tuberculous patients must be considered as a very important symptom of tuberculous infection. It should be studied in all its variations, according to the age

13. Courmont (Paul): Séro-prognostic des pleurésies, tuberculeuses, Jour. Am. Med. Assn., 1908.

14. Bendix: Ueber Séro-Diagnose der Tuberculose, Deutsch. med. Wehnsch., 1900.

of the patients, to the localization, form and extent of the lesions, and also in relation to other symptoms of infection or protective reactions.

II. In order that the results of such studies may be of value, the serum reaction must be sought for under definite conditions of technic as regards the choice of the culture, the method of its preparation and the technicalities of the reaction.

III. Recognizing the fact that the agglutinating power of the normal serum varies according to age and also with the animal species investigated, the serum reaction is of diagnostic value only when the agglutinating power of the serum is higher than that ordinarily observed in normal individuals of the same age and belonging to the same species.

IV. In serum diagnosis, for practical purposes, the serum reaction must be applied and interpreted with great clinical discrimination; its results must be compared with other symptoms and not interpreted blindly. It would be unwise to regard a patient as clinically tuberculous for the sole reason that his serum agglutinates Koch's bacilli. The reaction can have little or no diagnostic value unless there are other reasons justifying the suspicion of tuberculosis.

In such cases, however, a positive serum reaction is of great value. A negative reaction is of less value, as is generally the case with negative signs.

Diagnostically, the serum reaction may be considered from two different points of view:

1. The general reaction (with blood serum) does not give information as regards the location of the lesions; it indicates only that the system has been or is actually under the influence of tuberculosis. It will be the clinician's task to interpret this information and to derive from it conclusions concerning the location of lesions. The serum diagnosis will be of special use in children, in old people and also in adults suffering from chronic, torpid or latent forms of tuberculosis. Figures pointing to the frequency of latent tuberculosis in adults who clinically do not appear tuberculous are almost the same in the case of the serum reaction as with the tuberculin test (either subcutaneously or in the eye).

2. The local serum reaction depends on the agglutinating power of serous effusions and indicates the location of the lesions. It is particularly useful for the diagnosis of tuberculous pleurisy, and its results are in accordance with those that are given by inoculation or cytodagnosis.

V. As regards the nature and prognostic value of the serum reaction in tuberculous patients (serum diagnosis), as is the case in many other diseases, the agglutinating power of blood serum and other organic

fluids in tuberculosis, is proportionate to the power of resistance of the patients; furthermore, it is in inverse ratio to the virulence of the infection. The serum reaction is especially likely to be absent in very serious or very advanced cases of tuberculosis. It reaches its maximum height in cases which are in the process of healing. It may diminish or disappear sometimes before death; it can, on the contrary, increase when there is an improvement pointing toward healing or arrest of the disease. The character of the result of the test seems to be an index of the protective reaction of the system.

Practically, a study of the serum reaction and its relations may be of some prognostic value. In tuberculous pleural effusions, for instance, an increasing agglutinating power is of good prognostic import, while the failure of a reaction should prepare one for a fatal evolution sooner or later.

# STUDIES IN INACCESSIBLE INTERNAL HEMORRHAGES\*

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## I. THE EFFECT OF ADRENALIN ON INTESTINAL HEMORRHAGE

CARL J. WIGGERS, M.D.

DETROIT.

### I. INTRODUCTION

From a therapeutic point of view hemorrhages may be classified as *accessible*, i. e., those that can be directly influenced by drugs and *inaccessible*, i. e., those that can be influenced by drugs only through the circulation. In the former class come hemorrhages from the mouth, nose, throat, eye, wounds, etc., and such internal hemorrhages as can be reached by topical applications, viz., those from the uterus, urethra, bladder, stomach, rectum, etc. In the latter class may be listed intestinal, pulmonary, renal, uterine and cerebral hemorrhages.

The value of adrenalin in accessible hemorrhages is well recognized, but so far its use in inaccessible hemorrhages has been condemned rather than commended by our best therapists. The chief reason for this is the fact that adrenalin, when introduced into the vascular system, not only causes an active constriction at the point of bleeding, but also raises the blood pressure by a general constriction which tends passively to counteract the local influence and so augment bleeding. For this reason drugs that cause a fall of blood pressure have been recommended on the supposition that the pressure change would more than balance the local dilatation and so favor coagulation.

Unfortunately such a plan of treatment can not always be safely instituted. If the hemorrhage has already been profuse and the blood pressure is consequently low, or, if the hemorrhage is accompanied, as in surgical cases, by varying degrees of shock, it would be unwise therapeutics to lower the blood pressure still further; for it is as vital that the medullary centers should be sufficiently supplied with blood as it is important that the hemorrhage should be checked. In such cases it is necessary that the greatest portion of the remaining red blood corpuscles should be diverted from the channels where they are less needed, to the brain, where their presence is urgently demanded. The injection of saline solution accomplishes this only imperfectly, for the augmentation in pressure occa-

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\*The first of a series of contributions from the Research Laboratory of Parke, Davis & Co.

sioned by the increased volume is counteracted by the dilution of hemoglobin and the tendency to increased bleeding.

In precisely such vascular disturbances, when unaccompanied by hemorrhage, as in shock, it has been found that adrenalin accomplishes this better than any other drug. It is only the empirical assumption that it always causes an unfavorable increase in hemorrhage that prevents the use of what otherwise would be the drug of choice in hemorrhages accompanied by vascular failure.

Recent researches, however, have demonstrated reactions of blood vessels to adrenalin which caused prominent men to abandon this view and even advocate its use in such cases<sup>1, 2</sup>.

## II. REACTIONS SUGGESTING THE USE OF ADRENALIN

1. It has become a well substantiated fact that the reaction of normal blood vessels to adrenalin is of very brief duration. It is found, however, that the same dose which produces such a fleeting rise of pressure in a living animal causes a prolonged reaction when tested on a perfused organ from the same animal. The investigations of Meltzer showed that a prolonged reaction was also obtained in the body if the nerve supply to the vessels was cut. He<sup>1</sup> assumed that adrenalin affected blood vessels not only by a peripheral constriction, but that this tended to be neutralized and shortened by a central dilator action. When this central influence was interfered with in any way the peripheral constriction persisted for a longer time.

*Application.*—Assuming with Meltzer that the pathological process which caused the hemorrhage has also interfered with the nerve supply of the portion adjacent, it may be expected that the contraction at the point of injury will outlast the general rise of pressure and so tend to favor cessation of the bleeding.

2. It has been well demonstrated by perfusion experiments that the vessels of all regions of the body do not react equally to adrenalin. In some regions, as the intestines and kidney, its local action is great enough to counteract a considerable rise in pressure, but in other regions, as the brain, any local action is immediately overpowered by a small rise in pressure<sup>3</sup>.

*Application.*—It appears not unlikely that whole sets of vessels in regions susceptible to adrenalin may divert, by their contraction, the flow of blood to other regions less affected. Thus, in spite of a slight pressure rise, the flow of blood from ruptured vessels may lessen.

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1. Meltzer (S. J. and C.): *Am. Jour. Physiol.*, 1903, ix, 260.

2. Schaefer: *Brit. Med. Jour.*, 1908, ii, 1350.

3. Wiggers: *Am. Jour. Physiol.*, 1905, xiv, 452; 1907, xx, 106.

3. The effect of adrenalin on blood pressure is determined by the strength of solution, as well as by the rate and method of introduction into the body. It is possible, for example, to introduce adrenalin intravenously<sup>4</sup> in such weak solutions that the pressure rises only very slightly, or it may be introduced continuously so that this slight rise remains permanent<sup>4</sup>. Meltzer reported that given subcutaneously it caused either a slight rise or slight fall in pressure,<sup>5</sup> while given intramuscularly the rise of pressure occasioned was more prolonged though not so high as when given intravenously, and the fall was more gradual.

*Application.*—It is evident that the classical great and sudden rise of pressure of short duration which is immediately suggested by the use of adrenalin need not occur. In fact, the use of such doses is experimental, not therapeutical.

4. Adrenalin is reputed to increase the coagulability of the blood<sup>6</sup>. The application of this observation in facilitating clot formation need not be explained.

### III. PREVIOUS WORK ON INTESTINAL HEMORRHAGE

The value of adrenalin in inaccessible intestinal hemorrhages has not been the subject of many direct experiments. Lisin<sup>7</sup> recently investigated the subject experimentally. This worker rendered the blood of dogs non-coagulable by the injection of peptone, then created intestinal hemorrhages and estimated the degree of hemorrhages from time to time by determining the quantity of hemoglobin lost in definite time intervals. As a result of these studies he reported that intravenous injections of rather large doses of adrenalin caused a rapid and often instantaneous hemostasis, one that coincided with the rise in pressure and remained permanent after its fall.

Aside from the facts that the accuracy of the method of estimating the degree of hemorrhage is questionable,<sup>8</sup> and that the use of peptone causes severe circulatory disturbances, his research is open to a very practical criticism. He concludes: "Adrenalin does not really prove a hemostatic unless the vasoconstriction is accompanied by considerable slowing of the heart." Now it is well known that doses of adrenalin large enough to slow the heart act also to cause a cessation of respiration during the interval of action. Such doses when administered to patients have given

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4. Kretchner: *Arch. f. exper. Path. u. Pharmacol.*, 1907, lvii, 423.

5. Meltzer and Auer: *Jour. Exper. Med.*, 1905, vii, 59; *Am. Med.*, 1905, ix, 75.

6. Vosburgh and Richards: *Am. Jour. Physiol.*, 1903, ix, 39.

7. Lisin: *Arch. internat. de pharmacod. et de therap.*, 1907, xvii, 465.

8. Wiggers: *Am. Jour. Physiol.*, 1908, xxiii, 23.

rise to alarming symptoms, and in several instances to pulmonary edema. It is clear that these doses can never become practical in therapeutics.

This research was undertaken to test the influence of adrenalin in doses small enough not to affect either the rate of the heart or respiration.

#### IV. APPARATUS AND TECHNIC EMPLOYED IN THIS RESEARCH

In this research hemorrhages were created and changes in the outflow of blood recorded by a special form of apparatus, which did not necessitate the defibrination of blood and hence avoided the establishment of

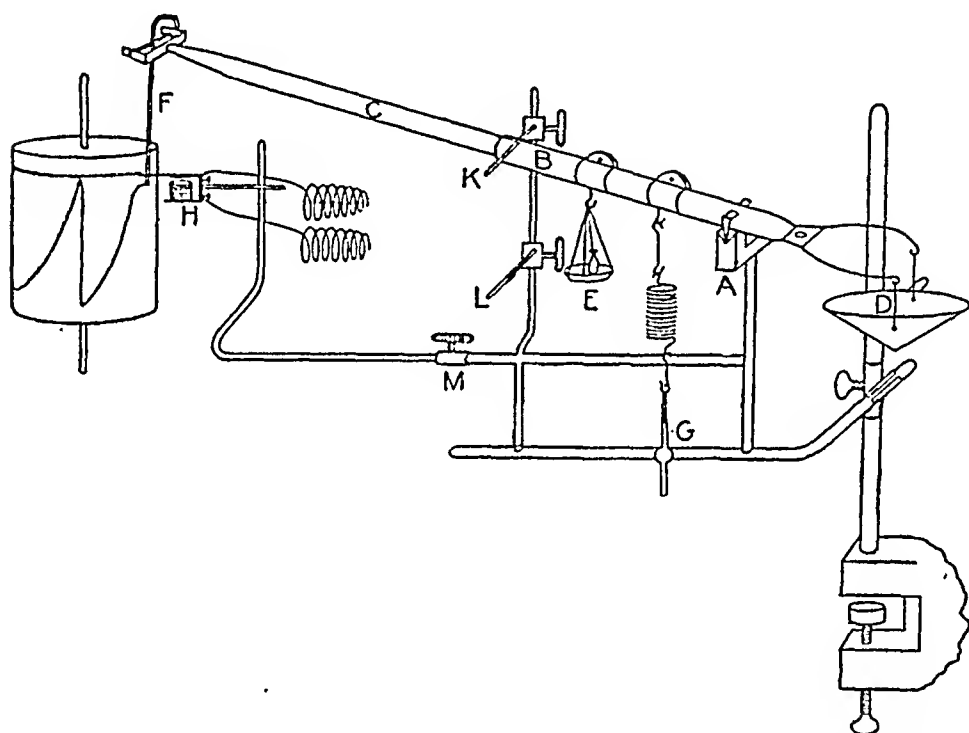


Fig. 1.—Diagram of hemorrhage-collecting apparatus. Letters referred to in text: H, a time signal; K and L, two stops, limiting the excursion of the aluminum beam C to range of drum.

abnormal conditions which such a process entails. The hemorrhage recording device (diagrammatically shown in Figure 1) has recently been described in detail<sup>8</sup>. As blood dripping from the wounded vessels above the apparatus is received into the dripping collecting pan (D) it causes the aluminum beam (C) on the other side of a knife edge (A) to rise and record on a smoked drum by a celluloid pointer (F) moving in a horizontal axis set in the end of a lever. When the lever has reached the top of the smoked paper the drip pan is emptied and another record started. On an evenly moving drum the pointer writes an oblique line

which becomes more inclined to the vertical or horizontal as hemorrhage increases or decreases (see subsequent curves). The apparatus is calibrated so that the actual quantity of blood lost can be estimated mathematically for definite time intervals. It possesses the further advantage that these intervals can be so chosen that outflow changes are not obscured.

Dogs were anesthetized as lightly as possible with morphin and chloretone dissolved in 40 per cent. alcohol. Canulæ were then inserted into the carotid artery and femoral or jugular veins. A small medium abdominal incision was made and a loop of small intestine with its mesentery was brought from the abdomen. With the intestine protected as much as possible by warm gauze sponges, silk ligatures were placed in loose loops around the mesenteric vessels as they passed toward the intestine. This completed, the intestines and mesentery, with the exception of the small portion where ligatures had been placed, were protected by gauze and the whole abdomen was surrounded by a rubber bandage. In the latter an opening was cut so as to expose the isolated vessels. The dog, with abdomen down, was then suspended in a hammock arrangement above the drip-recording apparatus before described. When the carotid pressure and respiration were being satisfactorily recorded, a mesenteric vessel was cut and the blood received in the drip pan and recorded.

#### V. THE NATURAL COURSE OF ARTERIAL INTESTINAL HEMORRHAGE.

In a study of the natural course pursued by an arterial intestinal hemorrhage attention was attracted to the fact that the initial amount of blood leaving the vascular system was not entirely dependent on the diameter of the vessels wounded, but varied rather in accordance with the product of this diameter and the pressure existing at that time. Thus the flow from a small artery could be as great as that from a larger one. From the time of its inception to its final cessation the bleeding diminished gradually, but more rapidly at the beginning than toward the end of its course, so that a plotted curve appears more or less concave to the abscissæ.

Comparisons of hemorrhages from various sized vessels (Fig. 2) show, furthermore, that the early diminution was much more rapid in hemorrhages from large vessels than in those from smaller ones, with the result that about three minutes after its beginning the flow from the larger and smaller arteries became nearly equal. This was due to the fact that the greater outpour of blood from the larger vessels not only caused the pressure to fall more rapidly, but also afforded increased material to favor clot formation over the wound.



The time elapsing before cessation finally occurred varied considerably. Sometimes the hemorrhage was checked within a few minutes with little fall in blood pressure. At other times it continued, as in the case of the experiment plotted in Figure 3, until the pressure became very low or death supervened. Experiments soon showed that this variation

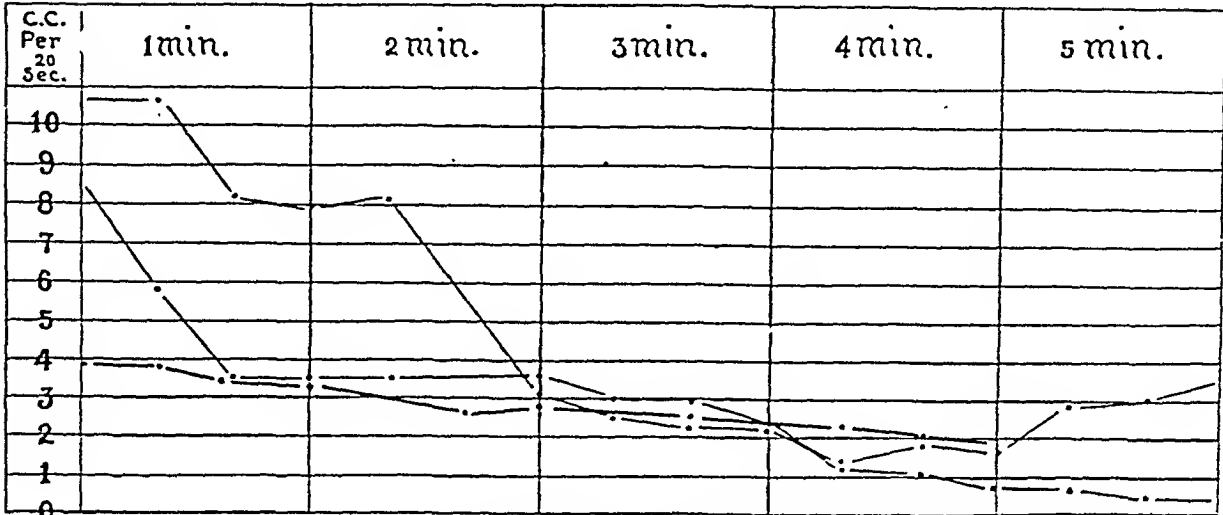


Fig. 2.—Three plots from Experiments 3, 10 and 4 respectively, showing the characteristic diminution of hemorrhage from large and small vessels.

in duration depended, not so much on the size of the vessel wounded, nor on the fall in pressure, as on the facility with which a clot formed over the wound. Observation of the process of clotting around a wounded vessel showed that blood flowing from a wounded artery does not begin to coagulate immediately at the point of hemorrhage, but on the tissues

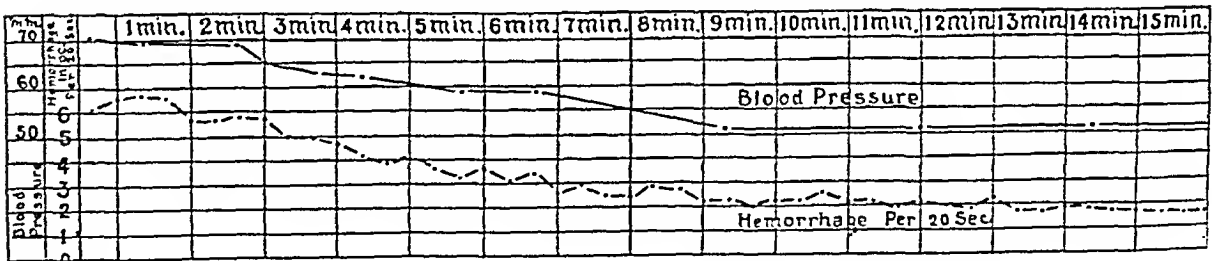


Fig. 3.—Plot from Experiment 1, June 24, 1908, showing effect of progressive hemorrhage on blood pressure..

at a distance. After an adherent clot had been formed there it was added to progressively until it reached and covered the source of hemorrhage. Then hemorrhage was checked. If the surface over which the blood could spread by gravity or other forces was great, the first clot formation occurred at a greater distance from the wounded vessel than if the

space over which it could flow was circumscribed in some way to the locality of the bleeding. With the technic employed the coagulating surface varied considerably in different experiments. Sometimes the mesentery was smoothly stretched, at other times gathered into folds with depressions between them. Sometimes the vessel was at the bottom, at other times at the summit of such a fold. This lack of uniformity was the cause of the varied duration of hemorrhages. One of the chief reasons that gastric and intestinal hemorrhages are not more frequently fatal is that the ulceration which causes the hemorrhage also supplies a mechanism for its rapid checking; viz., an excavation limiting the spread of blood.

#### VI. THE INFLUENCE OF ADRENALIN ON INTESTINAL HEMORRHAGES

After hemorrhage had progressed for intervals of time ranging from one to twenty minutes, adrenalin made up in solutions varying in strength.

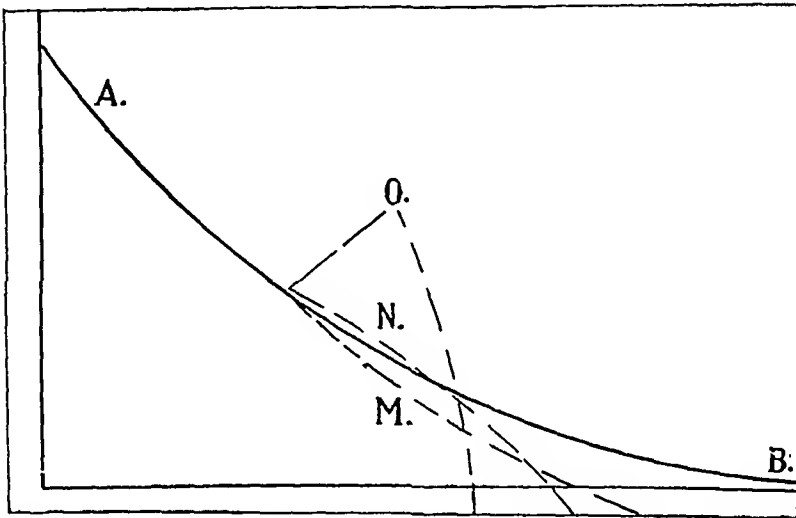


Fig. 4.—Scheme to illustrate the influence of adrenalin on the natural course of an intestinal hemorrhage. Description in text.

from 1 to 20,000 to 1 to 200,000 was injected in doses containing from 0.01 to 0.2 mg. ( $1/6400$  to  $1/320$  grain).

The results of these injections show that, under favorable conditions, the dose of adrenalin determines the effect on the course of hemorrhage much in the manner diagrammatically expressed in Figure 4. Every hemorrhage, as expressed by the arc AB, has a natural tendency to diminish and cease. A dose of adrenalin so small as to produce no effect may be administered during the course of the hemorrhage. The quantities from which the first effects are noticed undoubtedly cause a slight further diminution directly after injection. This shortens the course, as may be expressed by the arc M. As the dose of adrenalin is increased the dimin-

ution of hemorrhage seen is preceded by a temporary increase which, as larger doses are used up to a certain limit, becomes more and more pronounced. The diminution following the increase also becomes more pronounced and prompt after each larger dose, so that, though the injection is immediately followed by an even greater loss of blood, the course is actually shortened (are N or O). A dose is finally reached which causes no greater preliminary increase, but after which the diminution or cessation is equally prompt and certain. These results are illustrated by the curves shown in Figures 5, 6 and 7.

1. *Cause of the Preliminary Increase.*—Comparisons of the blood pressure records with those indicating the degree of hemorrhage show that the rise of blood pressure is responsible for the preliminary increase in the loss of blood. When only a slight rise of blood pressure is occasioned (Fig. 5) the local action of adrenalin on the wounded intes-

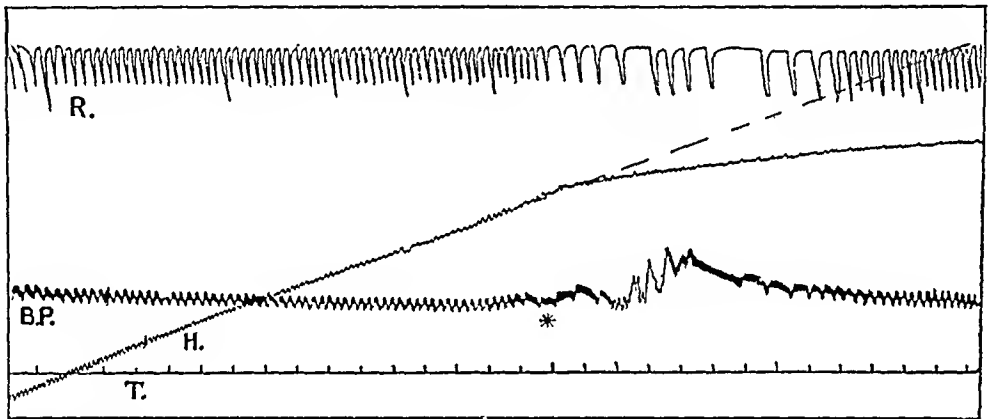


Fig. 5.—Segment of a record from Experiment 37, Aug. 7, 1908, showing the effect of a dose of adrenalin too small to cause an increase in hemorrhage, but large enough to cause a subsequent decrease. Blood rendered non-coagulable in this experiment. R, respiration; B P, blood pressure; T, time in intervals of 10 seconds, written on the base line for the present record: H, degree of hemorrhage recorded by hemorrhage-recording apparatus. Hemorrhage-recording apparatus wrote 4 mm. to the left of blood-pressure pointer. In all records of respiration the down-stroke represents inspiration, the up-stroke expiration. Adrenalin, 0.025 mg.

tinal vessels can apparently counteract it, but this local action does not increase proportionally with the rise in pressure, so, as the latter becomes greater, the preliminary increase follows (Fig. 6). The fact that extremely large doses cause no greater preliminary hemorrhage than smaller doses is explained by the fact that large doses slow the heart exceedingly, which keeps the pressure from exceeding a certain limit.

In dogs 0.01 to 0.025 mg. of adrenalin usually produced a satisfactory decrease in hemorrhage, while the preliminary increase in pressure

was so slight that, if any increase of flow preceded the decrease, it was very slight and transient. (Compare the rise of pressure and increase in outflow in Sections A and B, Table 1). Inspection of the preliminary increase occasioned in the experiments listed in Section C of this table will show, however, that this was not invariably slight and unimportant. This was because other factors than the actual dose must be taken into consideration in the administration of adrenalin.

A. The Variable Reaction of Animals to Adrenalin: Although the same dose of adrenalin causes practically the same relative rise in pres-

TABLE 1\*

Experiment.	Initial Outflow per 20 sec.	Dose of Adr.	Interval before Injection.	Diastolic. Blood Pressure			Actual Rise in Pressure.	Outflow of Blood per 20 Sec.			Preliminary In- crease, Actual.	Subsequent De- crease, Actual.
				Before.	During.	After.		Before.	During.	After.		
	c.c.	mg.	min.	mm.	mm.	mm.	mm.	c.c.	c.c.	c.c.	c.c.	c.c.
9A	5.8	.025	2½	32	36	32	4	2.3	2.9	2.4	.6	0
....	5.8	.025	4	32	36	32	4	2.4	2.5	1.9	.1	.5 A
12B	3.6	.025	3¼	37	42	38	5	2.4	2.9	1.4	.1	1.0
9A	5.8	.025	7	30	37	30	7	.9	.7	0	0	.9
20C	5.4	.025	3	33	40	32	7	4.8	5.4	1.0	.6	3.8
9B	4.2	.025	1	12	20	11	8	4.2	4.6	3.0	.4	1.2
....	4.2	.025	3	12	20	10	8	2.9	3.0	1.9	.1	1.0
12B	3.6	.025	14	35	46	38	11	1.5	2.5	1.0	1.0	.5
7C	1.5	.025	2	52	70	56	18	1.0	1.0	.7	0	.3 B
18A	5.4	.025	2½	56	70	54	14	3.7	3.9	.3	.2	3.4
7A	1.2	.025	3¾	54	86	54	34	1.3	1.9	.3	.6	1.0
7B	.9	.025	14	62	90	65	28	1.2	2.0	0	.3	1.2
12A	10.0	.020	5	64	70	64	6	5.2	6.7	4.7	1.5	.5
18B	6.5	.025	2½	48	60	44	12	2.2	5.4	.9	3.2	1.3
7D	1.1	.020	6	37	48	41	11	1.4	3.0	2.9	1.6	1.0 C
18B	6.5	.025	1½	48	74	42	26	4.2	8.7	2.2	4.5	2.0
19B	8.8	.025	11	38	72	35	34	8.0	5.0	2.0	2.0	1.0
19B	8.8	.050	5½	46	94	46	48	4.4	8.0	2.7	3.6	1.7
6B	3.0	.080	6	30	90	36	60	.2	1.9	0	1.7	.2
6D	0.8	.10	11	22	64	26	42	.1	.3	.1	.2	0 D
6E	0.6	.20	15	22	54	23	32	.2	.8	.1	.6	.1

\*The data comprised in this table have been selected as representative of a table listing the results of forty injections of adrenalin.

sure after each subsequent injection into the same animal, it is unfortunate that no such constant relation between dose and degree of reaction exists between various animals. It may be added that in these experiments care was taken to insure accurate dosage. Deterioration of the adrenalin solution was avoided by dissolving just before use a tablet triturate of adrenalin in the requisite amount of salt solution, and all injections were made with a graduated syringe after first filling the canula and connections with the adrenalin solution. Under these con-

ditions it was found that 0.025 mg. might cause any elevation of pressure between 4 and 34 mm. of mercury. (Compare Sections A, B and C of Table 1). It is not the purpose of this article to delve into the causes of this varied susceptibility of animals to adrenalin. It is merely necessary to point out the fact that human beings, as well as animals, may vary in their susceptibility. Thus reserve and caution demand that in the practical use of adrenalin not too much reliance should be placed on a definite dose and that its therapeutic use, for the present at least, should be accompanied by careful blood pressure observations.

Since such great variation in pressure results from a certain dose, corresponding variations must be expected in the preliminary increase of hemorrhage.

B. The Quantity of Blood Lost Before Administration of Adrenalin: The suggestion naturally arises that the amount of blood lost before

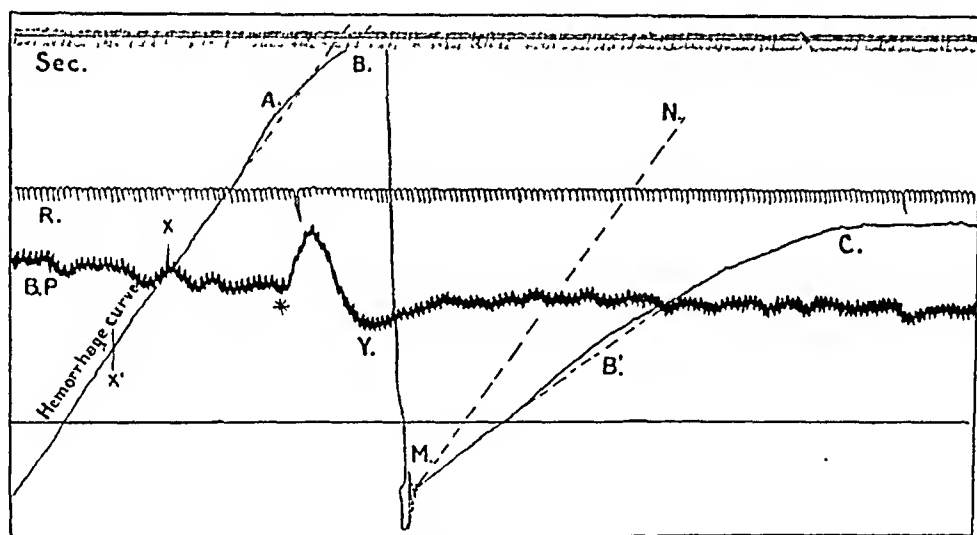


Fig. 6.—Segment of a record from Experiment 29, July 30, 1908, showing effect of a dose of adrenalin sufficient to cause a preliminary increase. The subsequent decrease occurs in several stages, A, B and C referred to in text. Lettering otherwise same as before. 1 c.c. = 4 mm. vertical rise.

adrenalin is administered may determine the degree of the preliminary increase. For example, it may be argued that, after a progressive loss of blood and a consequent lowering of pressure, adrenalin can not cause as great an increase of pressure as when injected while the pressure is higher. This is an important point to determine experimentally, for it leads to the assumption that larger doses may be employed when the pressure is low without incurring the risk of a greater preliminary increase. A comparison of the data, in heavy type, of Section B, Table 1, shows that, though small doses injected after much blood had been lost and the

pressure was consequently low, did not cause as great an increase in pressure as they did when injected early in an experiment while the pressure was still high, they exerted the same effect on the preliminary increase of hemorrhage. (Compare Experiment 9 B, 12 B, with Experiment 7 A, B, C, and 18 C). On the other hand, it was found that a large dose, for instance, 1 mg., induced a greater flow if given after hemorrhage had progressed for some time than if administered early (Fig. 8). This happened because the high pressure produced was powerful enough to dislodge the clot which had gradually formed and which was contributing to the checking of the hemorrhage.

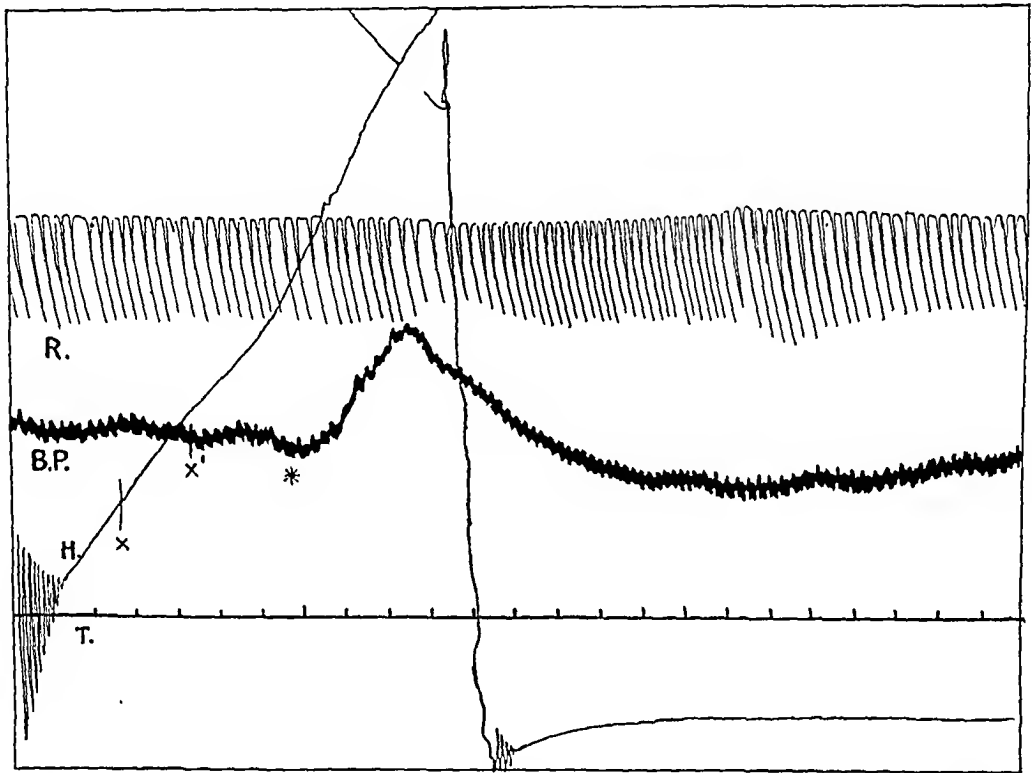


Fig. 7.—Segment of a record from Experiment 27, July 29, 1908. Effect of a large dose of adrenalin on pressure and hemorrhage. Lettering same as before. Adrenalin .05 mg.

The practical conclusion may then be emphasized that large doses must not be employed for fear of dislodging clots and thus seriously increasing hemorrhage. The slight rise of pressure caused by smaller doses is not powerful enough to dislodge the clot and they are therefore indicated late as well as early in the course of hemorrhage.

C. The Size of the Hemorrhage: Simple reasoning tells that a certain rise of pressure will cause a greater efflux of blood from a large than a small vessel, and so adrenalin seems fraught with greater danger in the larger hemorrhages. Experiments showed that while this is often

so it can be obviated to a great extent by a judicious choice of the time of injection (Section C, Table 1). As was previously pointed out, the amount of blood lost from large vessels is, within a few minutes after starting, no greater than from small ones, for the pressure in the former falls more rapidly and the opening is more speedily occluded by a clot than in a smaller vessel in which the pressure remains higher. Now, if a dose of adrenalin is injected early in the course of a hemorrhage, before this diminution has taken place it will cause a greater preliminary increase than a similar dose would from a smaller vessel. If, however, one waits with the injection until a diminution occurs, the absolute increase accompanying the injection is no greater than from a smaller vessel, provided the dose does not cause too great a rise of pressure. It seems reasonable to assume that by the time an injection can be given to a patient, the hemorrhage will, if from a large vessel, have diminished sufficiently so that its administration is not beset with excessive danger.

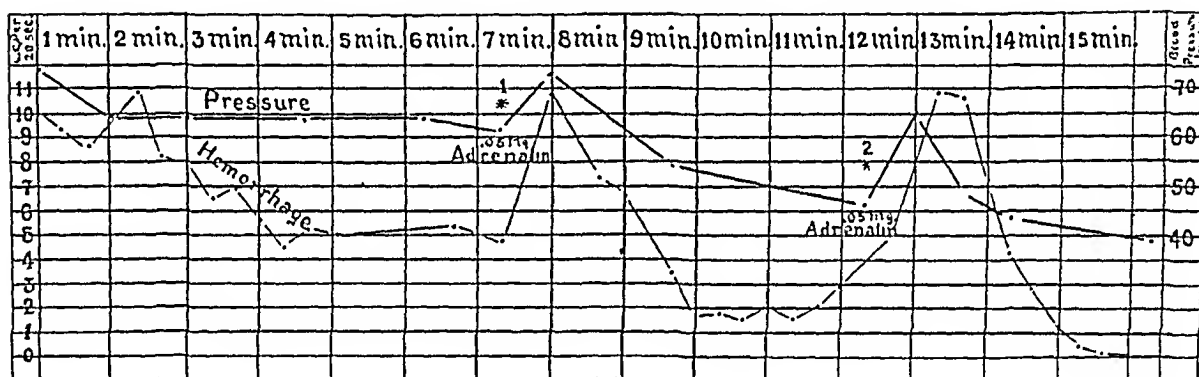


Fig. 8.—Plot from results of Experiment 12, July 9, 1908, showing relative effects of a large dose before and after formation of a coagulum over wounded vessel. Lettering same as before.

2. *Cause of the Subsequent Decrease.*—Following the preliminary increase of hemorrhage observed in forty experiments, adrenalin was found to cause an immediate cessation in 40 per cent. of injections, a marked decrease in 47 per cent., while in 13 per cent. no favorable action followed. It remains to analyze the causes of this subsequent decrease or cessation.

Figure 6 shows well the nature of those experiments in which cessation followed the use of adrenalin. Careful inspection of the record shows that this cessation occurred in two stages. After the increase of hemorrhage at A, a marked reduction below the normal followed instantly at B. This was followed by a final change to a cessation at C. In

other experiments the reduction at B was the same, but the final cessation at C was absent.

The first diminution was not due to the lowered pressure following the injection of adrenalin, as may be argued from the appearance of Figure 6, for it was more usual for the pressure not to be lower. It could also not be explained as a dynamic effect from the loss of blood for the following reasons:

1. Occasionally the diminution was absent after a preliminary increase (Experiment 9 A, 7 D), and again it was present when no preliminary increase had occurred (7 C, 18 A).

2. If the pressure and hemorrhage were augmented by stimulating the sciatic, the preliminary increase was occasioned by an elevation of pressure, but the subsequent decrease was absent.

The assumption then seems warranted that adrenalin acts longer at the point of injury than on the general blood pressure. This prolonged constriction caused the decrease in hemorrhage at B and this in turn favored clot formation, which caused the final cessation of hemorrhage at C. When adrenalin merely reduced but did not absolutely check hemorrhage, conditions for coagulation were not favorable around the opening. In order not to make this assertion without corroborating evidence several confirmatory tests were made.

In one series of check experiments the original technic of preparing the mesenteric arteries was retained, but the animal's blood was rendered non-coagulable by withdrawing at half-hour intervals a part of its blood, defibrinating it, and, after warming, reinjecting it into the jugular vein. In these cases hemorrhage diminished only as the pressure fell and cessation occurred only at the death of the animal. Adrenalin caused the same preliminary increase in hemorrhage followed by a decrease, but never by a cessation (Fig. 5).

In another series of cases the clot formation was interfered with by isolating each mesenteric vessel, doubly ligating it and cutting between the ligatures. To a short ligature left attached to the proximal end of an artery a light weight was attached, so as to place the vessel under a slight tension and draw it away from the mesentery. A lateral incision was then made in the vessel, as a result of which the blood passed down the thread in a pulsating spiral stream and dropped without touching the surrounding tissue. In this case the clot started to form at the place where the ligature was tied to the vessel, but the tendency for the clot to build up was counteracted by the downstreaming of blood. Adrenalin, administered under these conditions, practically reduplicated the curve shown in Figure 5. Absolute cessation never followed.



We may then conclude that adrenalin, by narrowing the lumen of blood vessels, can diminish hemorrhage after the rise of pressure has passed off. There is no proof that adrenalin can itself completely obliterate the vessels, however. The coagulating property of the blood is necessary to complete the action of adrenalin.

In regard to the 13 per cent. of cases in which adrenalin failed to diminish hemorrhage, it may be said that out of the five cases in which this occurred, in two (Experiments 6D, 6E, Table 1) the adrenalin was administered so late that the hemorrhage had already nearly ceased and hence no benefit could occur.

A. The Effect of Adrenalin on Coagulation of Blood: The question arises in this connection whether adrenalin also aids by actually hastening the coagulation of the blood. The frequent coagulation of blood in the cannulae during adrenalin experiments has been attributed to this factor by certain pharmacologists. The only research bearing on the problem was that of Richards and Vosburgh<sup>6</sup>. These workers report five experiments (one of which is absolutely negative) from which they conclude that adrenalin shortens the coagulation time as a result of its application to the pancreas.

The question was not extensively studied in this research and no permanent conclusions will be drawn. It may be stated, however, that as a result of many tests made on five dogs there was never the slightest indication that adrenalin, either when injected or added to the blood, appreciably hastened the coagulation process. A typical experiment is appended.

EXPERIMENT.—Aug. 20, 1908. Dog, anesthetized with morphin and chloretone. Carotid artery, jugular vein and femoral artery prepared and cannulae inserted into each, a very short one in the latter. After each test, the cannula in the femoral artery from which blood was drawn was rinsed with salt solution and dried with cotton swabs. For each test 1 c.c. of blood was drawn into a short test-tube, 7 mm. in diameter, and the time until the tube could be inverted without spilling, recorded. The observations follow:

Time.	Coag. Time.		Time.	Coag. Time.	
10:08.....	3.25 min.		10:40.....	Adr. 5 c.c.	1:100,000
10:11.....	2.75 min.		10:42.....	2.00 min.	
10:14.....	3.00 min.		10:45.....	3.00 min.	
10:18.....	3.00 min.		10:53.....	Adr. 5 c.c.	1:100,000
10:23.....	3.25 min.	4 gtt. Salt	10:54.....	3.00 min.	
	3.25 min.	4 gtt. Adr.	10:55.....	2.50 min.	
10:27.....	3.25 min.	4 gtt. Salt	11:00.....	3.00 min.	
	3.25 min.	4 gtt. Adr.	11:02.....	2.25 min.	
10:32.....	3.00 min.	4 gtt. Salt	11:05.....	3.00 min.	
	2.75 min.	4 gtt. Adr.	11:08.....	Adr. 5 c.c.	1:100,000
10:36.....	3.00 min.	4 gtt. Salt	11:09.....	2.75 min.	
	3.25 min.	4 gtt. Adr.	11:12.....	2.75 min.	

3. *The Value of Other Modes of Administration.*—The different methods of introducing adrenalin were investigated with the hope that perhaps the unfavorable preliminary increase in hemorrhage due to the high pressure occasioned could be eliminated or minimized, while the favorable decrease could still be retained.

A. Continuous Intravenous Injections: To produce continuous intravenous injections of adrenalin the solution was placed in a graduated burette and this was connected with the femoral vein. The rate of inflow was regulated by a clamp with a fine screw thread placed on the connecting tube, so that quantities of adrenalin from 0.06 to 0.005 mg. were introduced per minute.

TABLE 2.

Exp.	Rate of Injection per min. mg.	Duration of Injection min.	Effect on Pressure During Injection.	—Effect on Hemorrhage.— During. After.	
15A	.066	½	Rise 33	Marked Increase.	Cessation.
15C	.056	1½	Rise 20<62>22	Marked Increase.	Cessation.
15B	.04	3	Rise 22<28>12	Increase sl. Decrease.	Cessation.
15D	.028	3½	Rise 12>6	Increase.	Cessation.
15A	.02	4	Rise 15>6	Temporary Increase. Decrease.	Further Decrease.
15E	.018	3½	Rise 0>2	Decrease.	Decrease.
8B	.01	7	No change	Decrease.	Decrease.
25A	.008	4	Rise 4>0<2	Decrease.	Decrease.
25B	.008	4	Rise 5>3	Sl. increase Decrease.	Cessation.
25C	.007	4½	Rise 4>0<2	Decrease.	Decrease.

> means decreased to.  
< means increased to.

A glance at the results shown in Table 2 indicates that the doses of adrenalin exceeding 0.02 mg. per minute caused a considerable rise in pressure, which occasioned an increased flow as long as the introduction lasted. A great diminution or cessation of hemorrhage followed as soon as the injection ceased. Evidently the continuous administration of large doses possessed no advantage over instantaneous injections, while it had the disadvantage that the increase in hemorrhage was prolonged, whereas the real aim is to reduce the duration of the increase as much as possible.

Smaller amounts injected continuously during a definite time (0.007 to 0.01 mg. per minute) caused very little rise in pressure and little or

no preliminary increase in hemorrhage (Fig. 9). The diminution following compared favorably with that following single injections. The method of continuous administration is preferable in cases of hemorrhage accompanied by great vascular failure. In these it becomes of greater importance to maintain a higher pressure than to check hemorrhage quickly, and the fact that this can be done by adrenalin without augmenting hemorrhage is of great practical advantage.

B. Subcutaneous Injections: This method of administration was tested, but with negative results as far as the effect on blood pressure and hemorrhage were concerned. The reactions reported by Meltzer on rabbits could not be obtained in these experiments on dogs. It seems

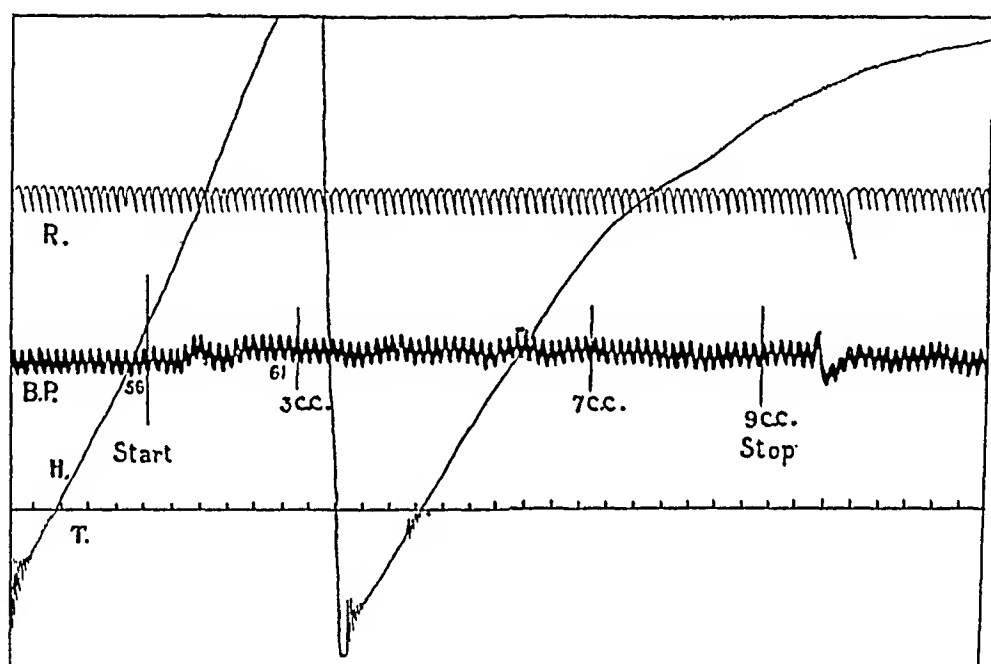


Fig. 9.—Segment of record from Experiment 25, July 27, 1908, showing effect of a continuous intravenous injection of adrenalin (1 to 300,000 at rate indicated on curve) on hemorrhage and blood pressure. Lettering as before.

certain, at least, that by this method not enough adrenalin enters the circulation to act efficiently on the blood vessels.

C. Intramuscular Injections: By deep intramuscular injections it is possible to introduce a desirable quantity of adrenalin into the blood stream. Seven experiments were made to determine the effect of adrenalin on intestinal hemorrhage when administered in this way. In each case from 0.5 to 5 c.c. of a 1 to 1,000 adrenalin solution was injected into the pectoral or dorsal muscles. The effect on hemorrhage much resembled that observed in continuous intravenous injections except, as

shown in Figure 10, the increase occasioned by the rise was converted into a decrease before the pressure fell. This occurred every time, even when a great rise in pressure followed an intramuscular injection. These favorable results and the convenience of the method favor its employment when hemorrhage is to be checked and the pressure increased. Larger doses are required when this method is used. In dogs 1 mg. given intramuscularly induces no greater effect on hemorrhage than 0.025 mg. given intravenously.

#### VII. THE EFFECTS OF NITRITES ON INTESTINAL HEMORRHAGE

Seventeen injections of nitrites were made during various stages of hemorrhage in order that their use might be compared with that of

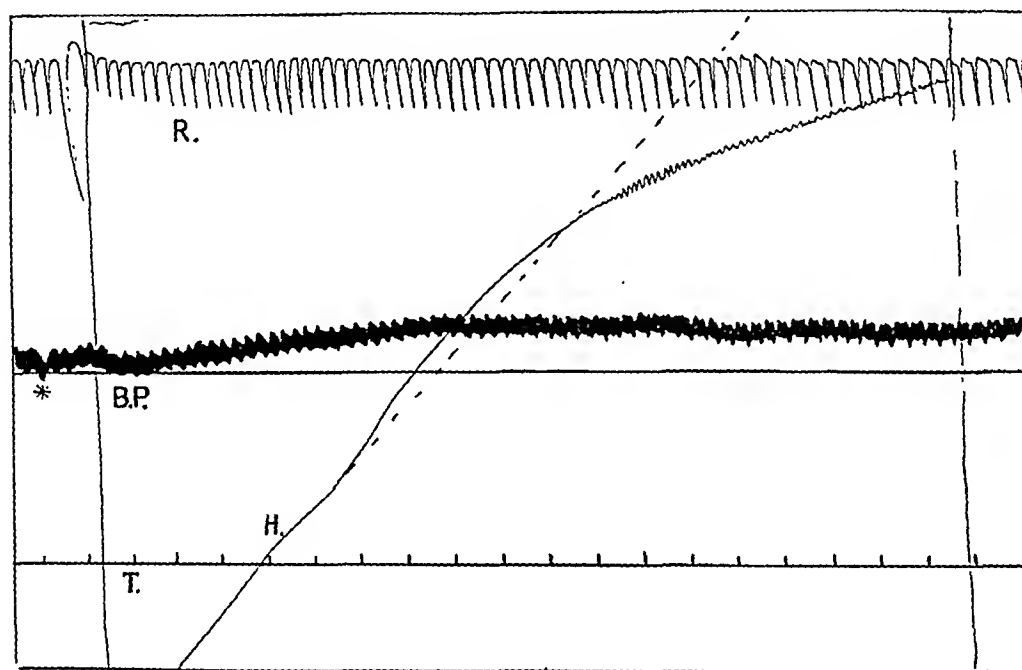


Fig. 10.—Segment of a record from Experiment 56, Aug. 27, 1908. Effect of an intramuscular dose of adrenalin on blood pressure and hemorrhage. Lettering as before. 1 c.c. adrenalin 1-4,000 intramuscular.

adrenalin. The results following the inhalation of amyl nitrite and the intravenous injection of nitroglycerin and sodium nitrite are incorporated in Table 3. Usually the nitrites caused an immediate fall of pressure, which was somewhat slower after inhalation of amyl nitrite than after the introduction of the others. In the case of amyl nitrite and nitroglycerin the fall was temporary, the pressure gradually returning to normal again, but in the case of sodium nitrite it remained low. The degree to which the pressure fell depended largely on the dose. The actual height of the pressure did not influence the relative fall.

In 76 per cent. of cases the fall of pressure caused an immediate diminution of hemorrhage. In 40 per cent. of these cases this was followed by a total cessation, even when the pressure returned again to normal; in 30 per cent. a further decrease occurred; while in another 30 per cent. the flow increased again to normal or above normal. When a total cessation or marked diminution occurred it was due to the fact that coagulation was favored by the lowered pressure; but when no such change took place the conditions for coagulation were unfavorable. A subsequent increase occurred only when the pressure returned to normal and a clot had not formed over the vessel. Even then hemorrhage had been temporarily benefited.

TABLE 3.

Experiment.	Drugs and Dose.	Initial Outflow per 20 sec.	Interval before Injection.	Diastolic Blood Pressure			Fall in Pressure	Outflow of Blood per 20 sec.		
				Before.	During.	After.		Before.	During.	After.
	Amyl nitrite.	c.c.	min.	mm.	mm.	mm.	P.C.	c.c.	c.c.	c.c.
GC	5 gtt.	2.9	7	26	23	26	11	.7	.5	.8
47A	10 gtt.	21.0	2 3/4	72	54	70	25	15.0	6.8	0
57A	5 gtt.	7.5	4	50	47	48	6	4.0	2.0	0
*58C	5 gtt.	3.0	12	28	23	25	17	3.0	3.0	2.25
....	3 gtt.	7.0	7 1/2	32	23	30	25	2.3	.7	.2
Nitroglycerine.										
33	1/250 gr.	3.7	5	100	70	90	30	3.3	2.5	1.0
....	1/100 gr.	3.7	12	84	56	79	32	1.0	0	0
34B	1/100 gr.	23.7	8	56	38	52	32	7.5	7.7	5.0
47B	1/100 gr.	23.6	3 1/2	50	34	49	29	8.3	7.2	0
50C	1/100 gr.	18.0	12	22	6	18	72	14.0	4.3	0
24B	1/100 gr.	6.4	12	22	15	22	31	6.0	2.0	1.4
Sodium Nitrite.										
54	2 1/4 gr.	16.0	3 1/3	54	22	22	60	11.8	4.5	2.3
....	2 1/2 gr.	16.0	12	22	18	18	13	2.0	1.5	1.5
*57C	3 gr.	3.0	9	22	14	14	36	2.0	0.5	.5
47D	15 gr.	14.0	2 1/4	28	16	16	57	13.0	.75	.75
48	10 gr.	11.2	6 1/2	92	33	33	64	2.0	1.5	3.0
49A	10 gr.	5.0	3 1/2	56	26	26	53	1.6	.5	.2

\* Blood rendered non-coagulable.

In 24 per cent. of cases the fall of pressure had no beneficial effect on hemorrhage. In two of these cases (Experiments 34 B, 47 B) the hemorrhage was from a very large vessel, and in the other cases the pressure had already been permanently lowered by previous administration of nitrites, so that subsequent injections caused only a slight fall.

It may be concluded, then, that nitrites, by the fall in pressure induced, cause an immediate diminution of hemorrhage, followed by cessation, if conditions for coagulation around the wound are favorable.

There is, however, a danger in lowering the pressure by the use of nitrites in cases in which hemorrhage has continued for long intervals of

time. This danger is not theoretical, but can be experimentally demonstrated. In three experiments after the pressure due to hemorrhage had become very low an injection of nitrites was made, which, by its fall in pressure, caused not only a diminution of hemorrhage, but also a failure of the respiration and the heart.

#### VIII. CONCLUSIONS

The following conclusions may be drawn regarding the use of adrenalin in intestinal hemorrhages:

1. Large doses of adrenalin (0.05 to 0.1 mg.) cause a short preliminary increase in hemorrhage followed quickly by a decrease or cessation

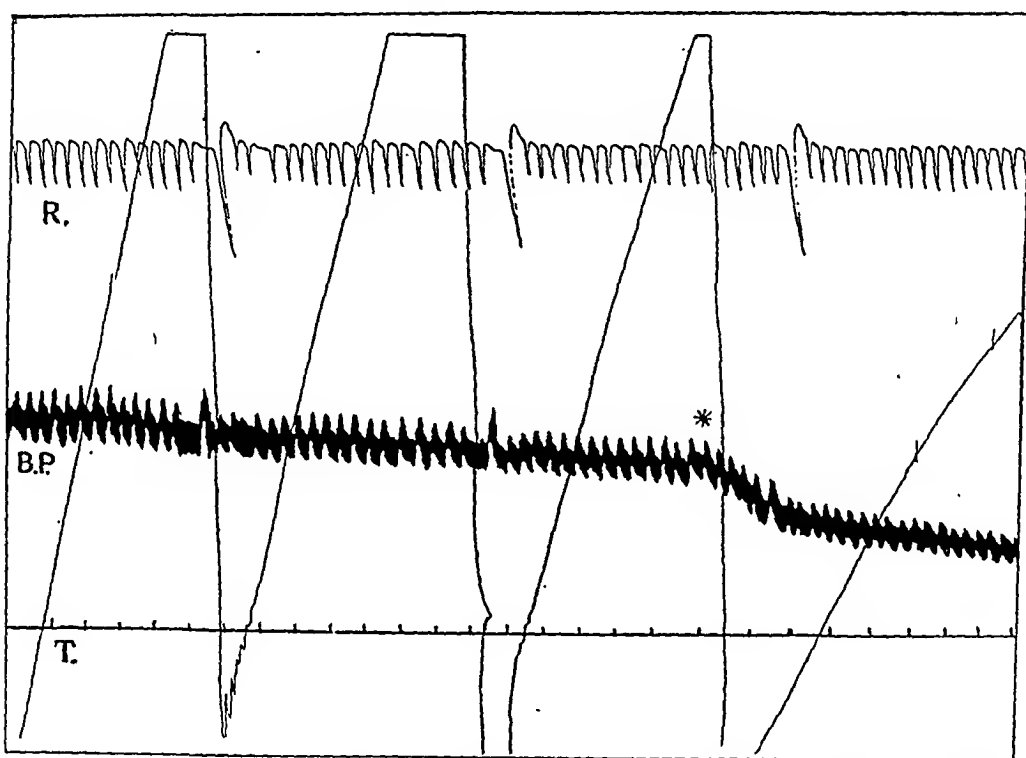


Fig. 11.—Segment of record from Experiment 57, Aug. 28, 1908. Effect of nitrites on blood pressure and hemorrhage.  $2\frac{1}{2}$  grains  $\text{NaNO}_2$ .

of bleeding. On account of the great preliminary loss of blood they are always contraindicated.

2. Small doses of adrenalin (0.01 to 0.025 mg.) cause little or no preliminary increase, but shorten the course of hemorrhage. As they save the red blood cells in every way they are therapeutically desirable.

3. The method of introducing adrenalin determines the effect on blood pressure and hemorrhage. No results are obtained by subcutaneous administration. By continuous intravenous injection of weak solutions a slight elevation of pressure can be maintained and hemorrhage

simultaneously checked. This can also be accomplished by intramuscular injections.

4. Adrenalin is not indicated in all intestinal hemorrhages. The condition of the blood pressure is the criterion for its use. In hemorrhages of short duration, when the pressure has not fallen to any extent, a judicious dose of nitrites proves of more benefit than adrenalin. When the bleeding has been profuse, however, and a low pressure already exists, it becomes vital that hemorrhage should be checked without further reduction of pressure. Adrenalin finds its use in this field.

5. The use of adrenalin should always be closely followed by blood-pressure observations. A dose sure to be below the safety limit should first be tried and the pressure carefully estimated. If no rise occurs gradually increasing doses may be injected until a slight elevation of pressure is present, in which case we may be certain that enough has been introduced to affect hemorrhage, and at least no significant preliminary increase has resulted.

## THE THERAPY OF DIABETES MELLITUS \*

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In the lecture which I had the honor to deliver a few weeks ago before the New York Academy of Medicine, I explained that human diabetes mellitus was a disease of highly complicated nature. I then took the stand that we should not seek in the pancreas the sole cause of the disease, but rather that a rôle is also played therein by other organs which elaborate internal secretions, and especially by the nervous system. In most general terms I defined the diabetic disturbance of metabolism as a lack of equilibrium between carbohydrate mobilization and carbohydrate combustion, arising from insufficiency of the pancreas or from overactivity of the chromaffin system, or from both causes together. Apart from the rare cases in which grave pancreatic disease has been found, we are at present ignorant of the ultimate cause of this disturbance of metabolism, and accordingly a causal therapy, the ideal therapy in every disease, is to-day out of the question. Symptomatic therapy seeks, in the first instance, to combat the most prominent symptom, the excretion of sugar and its results.

Theoretically two possibilities exist:

1. To increase the efficiency of carbohydrate metabolism. Conceivably this might be accomplished by increasing the internal secretion of the pancreas by the implantation of a new organ—until now a pious hope—or by the use of pancreatic secretion. Recently Zuelzer has reported such experiments, but to-day they do not possess practical value. Further, it may be expected that a diminution of the excessive carbohydrate mobilization should increase the utilization of sugar. This might be accomplished by checking the nervous system. The success which occasionally accompanies the use of sedatives may come about in this way. Unhappily such successes have been slight.

2. To diminish the requirements, thereby giving the diseased organ or organs the opportunity of recovering. This may be brought about by diminishing the amount of the food, especially of the most effective sugar-formers. This is the theoretical foundation of the dietetic therapy of diabetes mellitus, which has thus far been regarded as the sovereign means of treatment.

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\*Delivered before the Harvey Society, Nov. 28, 1908.



Before turning to the therapeutic measures which aim to improve the carbohydrate metabolism, I wish to consider a small group of cases which manifest a marked disease of the pancreas, for these often require a special therapy. When in such cases pancreatic disease has proceeded so far that there is no longer an adequate secretion of pancreatic juice into the intestine; or when, the more common event, lithiasis causes complete obstruction of the pancreatic duct, characteristic disturbances of absorption arise. These concern chiefly protein and fat. The very voluminous stools contain great quantities of neutral fat; microscopically the picture is mainly muscle fibers and fat droplets. In extreme cases the fat may flow out of the anus in an oily mass and stiffen into a butter-like paste. Salomon has pointed out that, in doubtful cases, by feeding large quantities of butter, such stools may be caused and the diagnosis established.

Such patients are in a grave condition; protein and fat are very imperfectly absorbed, while the carbohydrates are excreted, unutilized in the urine, as grape sugar. Therefore these patients are starving and they actually live on their own tissues and rapidly lose flesh. In such cases therapy is of great avail in replacing the pancreatic secretion. von Noorden first used the raw pancreas of the ox, but this preparation quickly becomes obnoxious, and accordingly pancreatic extract has been substituted for it. Since the acid gastric juice diminishes the activity of pancreas preparations, tablets hardened with tannin have been employed, in the expectation that they would not be disintegrated before reaching the intestine. This preparation, under the name of pankreon, is, however, not always active. According to our experience, the most successful preparation is the pankreatin of the Rhenania factory, in doses of 10 gm. daily; simultaneously, however, the diminished alkalinity of the intestine must be repaired. According to von Noorden, this may best be accomplished by the use of calcium carbonate, which is less readily absorbed from the stomach than sodium bicarbonate. Further, it may be mentioned that emulsified fat (milk-fat or egg-yolk) is much better utilized. With the help of this therapy in such cases the body-weight may often be readily increased, and for years together tolerable conditions for the life of the patient may be established.

I turn now to the disturbances of the carbohydrate metabolism. The chief end of dietetic therapy is here the depression of glycosuria. Of course, we must not attend to this factor alone; complicated acute infectious diseases may often cause a quite enormous increase in the formation of the ketone bodies; further, chronic infectious diseases, as, for instance, tuberculosis, may often, if not always, prevent a strict dietetic

treatment. In light cases of tuberculosis, however, an improvement in the tuberculous process is often to be observed with the disappearance of sugar from the urine. Indisposition of the gastrointestinal tract, often the result of a long-continued protein-fat régime, sometimes occupies a prominent position. Especially, however, does the occurrence of acidosis prohibit a decrease in the carbohydrate of the diet. This matter will be discussed later.

I wish now to present a question of fundamental importance. On what grounds do we seek to bring about a disappearance of glycosuria? Obviously by the excretion of sugar the food loses just so much of its value. For instance, in an extreme case, 500 gm. of sugar may be excreted in twenty-four hours; if this patient receives an ordinary diet, which yields 2,500 calories daily, he is losing through the excretion of sugar in the urine 2,000 of these calories; accordingly the patient is living on his own body and rapidly loses flesh. Such cases of extreme glycosuria are, of course, exceptional. In cases in which 100 gm. of dextrose are daily excreted, the loss of energy is only 400 calories, and these may readily be replaced by the equivalent quantity of fat, for instance, by 50 gm. of butter. Further, the circumstance that the protein-sparing carbohydrates are the substances here involved is not of essential importance. In my publications numerous instances are cited which show that often, in the most severe cases of diabetes with enormous excretion of sugar, a comparatively small addition of calories may prevent a loss of protein; and, indeed, that a tendency, thus far difficult to explain, to a retention of protein exists. The salient point accordingly depends on another circumstance, which may be formulated as follows: Glycosuria is a result of hyperglycemia, and in depressing glycosuria we seek chiefly to depress the hyperglycemia. In this connection there arise from the more recent investigations in von Noorden's clinic therapeutic considerations of great importance. Liefman and Stern have shown that in long-continued cases of diabetes mellitus, even with relatively slight excretion of sugar, very considerable hyperglycemia may be displayed; and that, after the disappearance of sugar from the urine in such cases, it may be a very long time before the sugar content of the blood has sunk to its normal level. Apparently after long-continued hyperglycemia, the kidneys lose their high degree of sensitiveness to slight increase in the sugar content of the blood. As an example, I present the following case recently observed in the clinic: With a daily sugar excretion of 5 gm. the blood sugar amounted to 0.36 per cent.; on the twenty-third day after the disappearance of sugar from the urine it still amounted to 0.123 per cent., instead of the normal content of 0.085 per cent.

We are accustomed to refer many, indeed most, of the secondary phenomena in diabetes to hyperglycemia: the lancinating pains, furunculosis, pruritus, the falling out of the teeth, the failure of hearing, the premature cataract, the impotence, the vulnerability of the tissues, and the early arteriosclerosis with gangrene. But the significance of hyperglycemia is far greater than this, in that long-continued hyperglycemia increases the disturbance of metabolism, thereby establishing a vicious circle! We understand accordingly why all these results of hyperglycemia, and one especially, namely, gangrene, are to be found even in apparently very mild cases of diabetes. These individuals may excrete a few grams of sugar daily, but they may have had diabetes and accordingly hyperglycemia for fifteen years; thus we perceive the desirability, even in cases of the diabetes of old age, of not being content when the excretion of sugar has been reduced to a few grams, but of insisting on complete disappearance of sugar. The understanding of many characteristics of tolerance is to be found in these relations; thus we often perceive that, even severe cases in youth, which may only with difficulty yield sugar-free urines, possess for a remarkably long time no tolerance for carbohydrates; indeed, we have recently observed such a case in the clinic, which, nine days after the disappearance of sugar from the urine, showed a sugar content of the blood of 0.21 per cent. So long, therefore, as the blood sugar has not attained its normal level no tolerance is to be expected. In cases in which a careful experiment in the feeding of carbohydrates produces an immediate excretion of sugar, it is well to remove carbohydrate entirely from the diet during several weeks. In the above-mentioned case it took two months, after the urine was sugar-free, to establish a slight tolerance, approximately 10 gm.

I turn now to the question how glycosuria is to be combated. There is in the literature an extensive accumulation of facts on the influence of various foodstuffs on glycosuria. I myself, with several collaborators, have been occupied with this problem during the past five years. The results of the older as well as the more recent investigations indicate that the disturbance of metabolism in diabetes is of a very complex nature, and that thus its intensity is subject to many factors. Each case has its peculiar characteristics and requires a special study; schematic treatment here would be quite out of place. Before determining on a plan of treatment, therefore, it is necessary to obtain an estimate of the character and intensity of the disease. In order to accomplish this, it is advisable to place every new patient for a period of three days on a test diet of known composition. At our clinic the following test diet is used: 250 grams of meat, 150 grams of butter, 4 eggs, 300

grams of vegetables with low carbohydrate content. In addition, tea, bouillon, coffee, about 4 deciliters of light white wine and 75 grams of white bread, divided through the day in three equal portions. This diet contains approximately 16 grams nitrogen, 50 grams carbohydrate and about 2,400 calories. Cases with severe acidosis and with signs of beginning coma are, of course, excepted; for these the carbohydrate content of this diet would be too low and thus be dangerous.

The sugar excretion on this diet can vary considerably. I have noted here some of the types:

	First Day.	Second Day.	Third Day.
Case 1—			
Dextrose, grams .....	30	10	5
Acetone .....	0	0	0
Case 2—Dextrose, grams—			
Titration .....	90	60	40
Polariscope .....	85	60	25
Acetone .....	+	++	+++
Case 3—			
Dextrose, grams .....	20	40	50
Case 4—Dextrose, grams—			
Titration .....	70	70	70
Polariscope .....	45	45	45
Acetone .....	+++	+++	+++
Nitrogen average = 15 grams.			

In Cases 1 and 2 we may assume that the patients had previously taken more carbohydrate than is contained in the test diet. Case 1 is a very mild one; the patient, in all probability, will become sugar-free on further treatment. Patient 3 probably has been previously on a strict diet. Patient 4 had probably been before on a diet similar to the test diet. In this manner we gain an approximate idea of the dietetic habits of the patient previous to beginning treatment, irrespective of the patient's own account. Furthermore, by means of this test diet we can obtain a quick diagnosis of the degree of ketonuria.

I take this opportunity to point out that in severe cases, with large amounts of beta-oxybutyric acid in the urine, polarization is quite inadequate in the quantitative determination of sugar. This is undoubtedly self-evident; nevertheless, it is often overlooked in practice, as well as in laboratories and pharmacies. Polarization before and after fermentation has the drawback that we must await the completion of the fermentation. Fehling's method requires considerable practice. It is practical, therefore, to employ a modification of Fehling's method, in which the unreduced copper is titrated back by means of potassium iodid and sodium thio-sulphate, in acid solution. The estimation by this method can be performed in ten minutes. It is not infrequent in severe cases, especially under strict diet, to observe differences of 30, 40, yes, occasionally even

50 grams between the figures obtained by titration and by polarization. This difference is also a measure of the amount of oxybutyric acid excretion, a better one than is obtained by the determination of the amount of ammonia, since the latter is influenced by the sodium therapy and is dependent on the degree of protein metabolism.

From the difference between the titration and polarization and from the intensity of the acetone test and ferric-chlorid reaction, we may obtain during the three days' test diet an idea of the degree of ketonuria. Thus we see in Case 1 that the patient becomes almost sugar-free without the appearance of acetoneuria. This is a very mild case. In Case 2 the sugar falls off rapidly, too, but the ketonuria rapidly increases and warns us to be careful. Case 4 is stamped from the beginning as a severe one by the character of glycosuria and ketonuria.

In judging a case further, the intensity of the glycosuria is of great importance. We consider, in this respect, chiefly the third day of test diet, as it may be assumed that by this time a condition approaching equilibrium has become established. A sure opinion of the intensity of the glycosuria can be obtained only when we know, not merely the carbohydrate content of the food, but also its other constituents, since the sugar may be derived from various sources. In Cases 1 and 2 the sugar excretion is less on the third day than the carbohydrate intake. In Case 3 intake and output are about equal; in Case 4 the sugar excretion is some 20 grams higher than the carbohydrate intake.

Next in importance as a source of sugar is the burned protein. Furthermore, there are, indeed, cases in which the sugar excretion is so great that even the burned protein does not suffice for an explanation. In these cases we have no alternative for the present but to assume the formation of sugar out of fat. In these cases we observe occasionally, also, that a very large fat intake will increase the sugar excretion. However, these cases are relatively rare. In the great majority of all cases, the sugar excretion is determined by the carbohydrate and protein content of the food.

For our fourth case, now, as has been mentioned, the sugar excretion exceeds the carbohydrate intake by 20 grams. We have here a so-called negative carbohydrate balance of 20. This terminology is, however, inexact, because it overlooks the protein metabolism. It has an entirely different meaning according as 10 or 30 grams of nitrogen are simultaneously excreted in the urine.

One obtains, therefore, a better conception of the conditions through the ratio D:N. In Case 4 this factor equals:

$$\frac{70-50}{15} = 1.33.$$

One must not, however, assume that in this case only 20 grams of sugar are derived from the protein metabolism. On the contrary, it is much more probable that, in severe cases, the protein and carbohydrate are implicated according to their sugar value in the formation of urinary sugar. If we assume the sugar value of albumin to be 80 per cent., then for every gram of nitrogen in the urine there are 5 grams of dextrose. The sugar value of the metabolized material accordingly amounts to the carbohydrate intake plus five times the urinary nitrogen, and the coefficient of excretion is:

$$\frac{D \ 100}{\text{carbohydrate} + 5 \text{ N.}}$$

In Case 4 this coefficient amounts to:

$$\frac{70 + 100}{50 + (5 \times 15)} = \frac{7,000}{125} = \frac{48}{1}$$

That is, 48 per cent. of the sugar value of the food was excreted and 52 per cent. was assimilated. If the excretion coefficient rises over 100, and in consequence the ratio D:N rises over 1 to 5, then this indicates, in my opinion, sugar formation from fat.

Since we know the exact composition of our test diet, we can calculate the intensity of the sugar excretion according to this formula with accuracy. Since nitrogen retention frequently occurs in diabetes, it is desirable to determine the nitrogen content of the urine of the third day. By our test diet we have, then, determined the intensity of the glycosuria and ketonuria. If, in addition, the age, occupation, surroundings, the duration of the diabetes and possible complications are considered, we may arrive in the space of three days, with comparatively simple means, at a fairly clear idea of the intensity of the disease, which is of great advantage in forming a plan of treatment. A definite opinion, however, can be reached, it is true, only in the course of further treatment. It is dependent on the answers to the following questions: Can the patient be made sugar-free? Can a sugar tolerance be established? What is the course of the ketonuria?

We enter, then, into the second phase of the treatment; we attempt to render the patient sugar-free. In the mild cases it usually suffices to strike out the bread from our test diet. Thus it is to be expected, in Cases 1 and 3, that the urine will be sugar-free after a few days. In the severer cases it is necessary, in addition to the withdrawal of carbohydrates, to limit the protein intake. This is readily to be understood in view of what I have said before. The sugar value of our test diet

amounts to  $15 \times 5 + 50 = 125$ . Let us assume that the patient's sugar tolerance in Cases 1 and 3 is at 90; after the withdrawal of carbohydrates from our test diet we obtain a sugar value of 75, which is below the limit of the present tolerance; the glycosuria ceases. In Case 2 let us assume the limit of tolerance to be 50. We reach a level below the limit of tolerance then only if, in addition to the withdrawal of carbohydrate, we diminish the protein content of the food by at least 5 grams of nitrogen. This method is of considerable advantage also in the severe cases. In Case 4 there are, during the time of the test diet, 70 grams of dextrose in the urine. We now withdraw the carbohydrates and find, after two or three days, 36 grams. We could thus assume that the ability to assimilate the carbohydrate had diminished. However, if we take into account the sugar value of the protein, we obtain, in the first period, a total sugar value of 125 and a coefficient of 48; in the second period, a total sugar value of 75, and thus the same coefficient of 48. Thus there has been no change. It is true that such conditions are found only in very severe cases. In the great majority of all cases, the power of utilization rises rapidly with the diminution of the total sugar value, for less sugar passes through the body in twenty-four hours, the glycemia decreases and recovery begins. The consideration of the total sugar value, therefore, always gives us a much clearer conception of the conditions than the carbohydrate content of the food alone. The same is true of the carbohydrate tolerance. I propose, therefore, that the tolerance be also expressed in terms of the total sugar value.

In practice we proceed as follows: If the withdrawal of carbohydrate alone does not suffice, we decrease the nitrogen content of the food to about 8 grams and increase the amount of butter to about 200 grams. The patient should not lose weight during the process of becoming sugar-free. The sugar value amounts now to only about 50. If this also proves insufficient, it is advisable to introduce one or two days of vegetable diet; or, according to Naunyn, one day of fasting; or else one tries an oatmeal cure, to be discussed later.

At this stage of the treatment a very close watch on the ketonuria is necessary. The formation of the ketone bodies depends, as you know, on the lack of combustion of carbohydrates. Ketonuria may be produced even in the normal person by means of inanition or an exclusive protein and fat diet. The fact that much higher grades of ketonuria appear in diabetes is easily understood, since here there is also a failure to consume the sugar arising from the katabolism of proteins. Von Noorden has pointed out that diabetics may show very different degrees of ketonuria. Although they are on the same diet, they may show the

same amount of sugar in the urine and assimilate, therefore, the same amounts of carbohydrates. We have often observed this phenomenon in patients taking our test diet. We can assume with a fair degree of certainty that those with a higher degree of ketonuria have had it for a longer time. I am led to this conclusion by the fact that it is necessary to give more carbohydrates to suppress a ketonuria already existing than to prevent the occurrence of ketonuria (Satta). We ought, therefore, to try either to prevent the occurrence of ketonuria or to avoid an increase of one that is already present. Unfortunately this is not possible in most cases, if we wish to render the patient sugar-free. If on the test diet there is a marked ketonuria, and in particular a large amount of beta-oxybutyric acid in the urine, it is best to reduce the carbohydrates very gradually. The appearance of a considerable degree of ketonuria, however, need not cause anxiety, provided that one prevents acidosis; that is to say, the storing up of ketones in the body. Acidosis, once present, is often hard to get rid of and is dangerous under all circumstances. The fundamental point in the treatment, therefore, is to hinder the occurrence of acidosis. This is accomplished by the administration of alkalis, which render the ketone bodies capable of excretion with the urine. We should, therefore, always give sodium bicarbonate during the period of withdrawal of carbohydrates. In cases with a well-marked ketonuria one often sees that, with the beginning of the alkaline treatment, the difference between the figures for sugar obtained by titration and by polarization rises immediately and remains increased for several days; a sign that beta-oxybutyric acid is being flushed out of the body. The reaction of the urine affords an excellent sign as to whether you have got the better of the acidosis. If it becomes alkaline, you may be sure that you have neutralized the acids. In severe cases, 40 or 60 grams or more are necessary, and in diabetic coma more than 100 grams are often insufficient. If a marked ketonuria is present, it is better not to begin with small doses, but to saturate the body with alkali at once. As soon as the urine has become alkaline, the dose may be gradually decreased, just sufficient being given to keep the urine slightly alkaline. We usually replace a part of the sodium bicarbonate with the citrate of soda.

In cases with a high degree of acidosis, the administration of alkalis alone is not enough; we must endeavor to influence the formation of ketone bodies directly. Large doses of alcohol decrease the formation of ketones, but only to a slight degree. All other non-carbohydrate substances are either without effect or their action is dubious. The only efficacious substances are the carbohydrates. If, however, we give large



amounts of these, we increase the hyperglycemia and run the danger of damaging the power to combust carbohydrates, which is already defective. On the other hand, a reduction in the carbohydrates may cause a fatal coma; here we are truly between Seylla and Charybdis. In these cases it seems to me very important to reduce the food to a low point; for both fat and protein cause the production of large amounts of ketones, as has been shown by the excellent investigations of Allard, from Minkowski's clinic. The introduction of a "hunger day" in such cases has reduced the ketones in the urine to a third or less of what they were before. If, now, to the fasting patient fat or protein was given, the amount of oxybutyric acid rose at once 20 grams and more. It is, therefore, best to give a very low diet, containing from 8 to 10 grams of nitrogen and not more than 150 grams of fat and, in addition, 100 or 150 grams of carbohydrates in the form of fruit, milk, oatmeal, and so forth. As soon as one has decreased the formation of the ketone bodies and has provided for their prompt excretion by means of the administration of alkalies, one may for a short period also decrease the amount of carbohydrates (by means of two or three "vegetable days," with 50 grams of carbohydrates), in order to produce at least a temporary decrease of the hyperglycemia. Similar tendencies are seen also in the modern treatment of gout and acute nephritis, where we give the diseased organs time for recuperation by means of purin-free and non-nitrogenous diets, respectively.

When, in spite of careful treatment, the first signs of coma appear, prompt action is imperative. The patient becomes sleepy, loses his appetite, and complains of a sense of oppression in the chest; frequently there is a decrease of the excretion of beta-oxybutyric acid, and showers of casts appear in the urine. Such patients show almost constantly a marked degree of lipemia, even when fasting. One can easily show this by centrifugalizing a small amount of blood in a U-shaped capillary tube; the serum then appears milky. Very large doses of alkali are necessary here, in order to remove the enormous amounts of acid which are contained in the blood and tissues; 100 grams of sodium bicarbonate dissolved in a large amount of an alkaline mineral water are given during the course of the day. The diet should be easily digestible and consist almost exclusively of carbohydrates; it may contain 50 to 100 grams of levulose. If the patient is no longer able to swallow, the levulose may be given subcutaneously, dissolved in a liter of physiologic salt solution. The best method, however, is the intravenous infusion of a liter of 4 per cent. soda solution. Sometimes the patient comes out of the coma even during the infusion. Last spring I saw a patient who was

alive three months later, when I left Europe. I do not, however, know of any instance of recovery from a second attack of well-marked coma under this treatment.

Let us now return to the treatment of those patients who have become sugar-free through the withdrawal of carbohydrates, with or without the reduction of the proteins. This is the third stage of the treatment, in which we are to keep the patient free from sugar, and then to determine his tolerance and regulate his mode of living. It is advisable to follow Naunyn's suggestion and keep the patient two weeks to the diet on which he has become free from sugar. Then, in a mild case, one may begin at once with the addition of bread, which may be increased every three or four days until the limit of tolerance is reached. Then you may give half the amount tolerated, introducing variety in the bill of fare by means of fruit, cream, vegetables richer in carbohydrates, various kinds of bread, and so on.

In those severe cases, in which the reduction of the proteins is necessary to cause the disappearance of sugar from the urine, one should at first increase the nitrogen in the diet up to 12 or 14 grams. Afterward three or four weeks after the disappearance of sugar, carbohydrates may be added. In practice it is very important not to rely too closely on the amount of carbohydrates in various foods, as shown by the tables of equivalents. This is true of all forms of diabetes, from those which can not be rendered free from sugar down to the very mild ones. Different diabetics do not show the same degree of tolerance for different kinds of carbohydrates; one must try out each form of carbohydrate in the individual case. In this connection, we often see that levulose is borne in many light cases better than glucose; for this reason fruits rich in levulose are much preferable to those containing grape-sugar. Under long continued use of levulose, however, the tolerance for sugar usually sinks rapidly. Furthermore, I have seen cases in which there was a special sensitiveness toward levulose. The same is true also of milk; a few diabetics will not stand milk. I have recently seen a case in which administration of 250 grams of milk increased the glycosuria markedly and for a period of days. Further, it is an interesting fact brought out by our investigations with various sorts of sugar that maltose always caused the greatest increase in the glycosuria. This agrees with the empirical fact that diabetics do not stand beer well; it is best to forbid it. This point, however, is of less importance in America than in Germany. Of the substitutes for bread, I think the most important is *Luftbrot*, a very porous gluten bread, of which a loaf the size of two fists weighs only 30 or 40 grams. It contains, therefore, very little carbohydrate in

proportion to its bulk, and is not intended to replace bread, but to serve as a means of getting in cheese and butter. It is well to be very cautious in the use of the various substitutes for bread. Both the public and the physician are often deceived by the name "diabetic bread," and even by the analyses which are given on the label. I myself would not order any of them unless reliable analyses were at hand. Finally, I have to mention the special milk for diabetics which is prepared by many firms, and especially preserved fruits containing little sugar.

Especial care is necessary in the treatment of those cases in which the withdrawal of carbohydrates and the reduction of the proteins is not sufficient, and the sugar disappears from the urine only after the introduction of "hunger days" or "oatmeal cures." In such cases, even weeks after the disappearance of glycosuria, small additions of carbohydrates, or even an increase of the proteins, causes the reappearance of sugar in the urine. I have already called attention to the fact that here hyperglycemia may remain for a long time after the disappearance of sugar from the urine. I have seen in recent years three such patients, two of whom were young people of 16 and 20 years, and the third a man of 35, who, when he came under my care, had not been free from sugar for a year. In the case of the 16-year-old boy, even an addition of butter to the diet caused the appearance of traces of sugar. The three patients had at first well-marked ketonuria, and one of them excreted 22 grams of beta-oxybutyric acid. I kept these patients over three months on a diet free from carbohydrates and containing only a small amount of protein, and then added half a *Luftbrot* and later preserved fruits containing little sugar. Six months later they were still free from sugar and able to do their work, and the ketonuria had disappeared. Such rigorous treatment demands great energy on the part of both patient and physician. When, however, we consider that in such cases with the reappearance of sugar and hyperglycemia the disease usually takes a rapidly downward path, and, therefore, the acquirement and maintenance of a condition free from sugar is a question of life and death, the self-denial of the patient and the labor of the physician are amply repaid.

All the measures against glycosuria previously mentioned had the common property of reducing the sugar value in the diet. From this principle the following carbohydrate cures differ widely. The milk and potato cures I can dismiss with a few words. The first diminishes the glycosuria only when diabetic patients, formerly overnourished, are insufficiently nourished on strict milk diet. Indeed, in many cases, in spite of undernourishment, milk diet can even increase glycosuria. The

potato cure is considered by nearly all experienced physicians to be without value. On the other hand, I must go somewhat more into detail regarding the oatmeal cure, since it is of both theoretical and practical value. As you know, this treatment was recommended by von Noorden first at the meeting of the German scientists in Carlsbad. In an article shortly to appear I shall describe fifty cases, of which I have personally observed eight in my wards; the others Professor von Noorden has reported to me from his private practice. From all the results in these cases I can single out only a few important points. First, I must describe our present method of giving the oatmeal cure. After several days of strict diet come two vegetable days, then three oatmeal days, and lastly two vegetable days. On each oatmeal day the patient receives 250 to 300 grams of American oatmeal, prepared with an equal amount of butter and divided into five meals; and, in addition, black coffee, wine, a little brandy and, when necessary on account of diarrhea, a few drops of tincture of opium. Frequently when the first trial was unsuccessful, we have obtained good results from an immediate repetition of the oatmeal days following the last vegetable days. After the vegetable days we give strict diet with very little (diminished) protein. I may express the results in short as follows: In a certain proportion of the cases (about 10 per cent.) the success can be called really remarkable. These are severe cases with ketonuria which it had formerly been impossible to make sugar-free either by completely removing the carbohydrate from the diet, or by a low protein diet, or by a strictly vegetable diet. In these cases the sugar and ketone bodies disappeared from the urine during the oatmeal days or the following vegetable days, and the patient could subsequently be kept sugar-free. For a second group of cases the sugar entirely or almost wholly disappeared, but later reappeared on the return to a protein diet. In a third group of severe cases the glycosuria remained high or even increased; nevertheless, the influence on the ketonuria was remarkable. Finally, we have seen a few very severe cases, in which there was no assimilation of the oatmeal and, therefore, no influence on the ketonuria.

For a thorough understanding of the effect of the oatmeal the following points must be noted: The sugar value of an oatmeal day is 200 grams, 175 from the carbohydrate and about 25 from the protein of the oatmeal. The sugar value of our test diet is 125 grams, that of the carbohydrate-free diet only 80, that of the diet with restricted protein is about 50, and that of a vegetable day is still less. Therefore, if we see that in some cases during the preliminary vegetable days 20 or 30 grams of sugar are excreted daily, disappearing, however, during the oatmeal

days, this result is truly astonishing, and it can be readily understood that through the assimilation of such an enormous quantity of carbohydrate the ketonuria often diminishes from about 40 grams almost to nothing, and the output of ammonia becomes normal. Let us take, however, a case in which the average sugar output increased from 30 grams on the vegetable days to 40 or even 60 grams on the oatmeal diet; even in such cases the marked effect on the ketonuria is readily understood, for, on each vegetable day, of the entire sugar value only 20 grams are assimilated; whereas, on each oatmeal day, from 140 to 160 grams are assimilated. We must, then, consider as the essential result of the oatmeal cure the fact that we are enabled to bring about the assimilation of a considerable quantity of carbohydrate, and thus to diminish the ketonuria without increasing too greatly the hyperglycemia. What is very remarkable in this connection is the fact that, with other carbohydrates similarly used, we do not get the same result.

In my report I shall mention a case in which 30 to 40 grams of dextrose were excreted daily during the oatmeal cure, while on a diet consisting of potatoes, milk, zwieback, fruit, etc., an average of 150 grams of sugar appeared in the urine. In another case, a diet of wheat flour was given between two periods of oatmeal diet. The difference in the sugar excretion was almost as great as that in the case mentioned. The most important indication for the oatmeal cure, therefore, is the combating of ketonuria; and the fact that some apparently hopeless cases also become sugar-free is a welcome additional occurrence. A further indication for this cure is in cases in which the digestion is impaired by a too long-continued meat and fat diet.

Some authorities have belittled the advantages of the oatmeal cure. Naunyn, for example, believes that the apparent good effect on the glycosuria is brought about by a fermentation of the greater portion of the oatmeal in the intestine. He uses as an argument the results of the investigation of his pupil, Lipitz, who found the intestinal bacteria increased in numbers during the oatmeal cure. This objection, however, does not hold. In the first place, Lipitz's method of quantitative estimation of the bacteria is not reliable. Second, there is practically no clinical evidence of a pronounced intestinal fermentation — no tympanites and no fermenting stools. Third, if there were much fermentation, as Naunyn claims, the effect on the ketonuria could not be explained, for the fermentation products of carbohydrate, since they can not again unite to form sugar in the body, should rather increase the ketonuria, as, for instance, in the form of low fatty acids. The fourth and most striking point is with regard to the protein metabolism. The

nitrogen output amounts, in successful cases, on oatmeal days, to only 5, 4 or even 3 grams, and, indeed, is sometimes less than the so-called minimum nitrogen determined by Landergreen in normal individuals, kept for several days on a practically nitrogen-free diet, rich in carbohydrate. Such low nitrogen outputs during the oatmeal cure are possible only when the carbohydrates are really assimilated, and not merely fermented in the intestine. In such cases also we find regularly an increase in body-weight of two kilos or even more in three or four days. The final test of our assumption is to be found in those few cases in which the oatmeal is not assimilated at all, as shown by the enormous output of sugar while on this diet, for there is no effect on the ketonuria and the nitrogen output amounts to 8 grams or even more daily.

The cause of this remarkable effect of oatmeal is as yet unknown. That it is not the limited amount of protein in the diet is shown by the fact that von Noorden formerly added large amounts of vegetable protein to the oatmeal porridge, deriving, however, good results. Furthermore, this assumption can not explain why other carbohydrates do not produce the same result when given in the same way. The argument that the cause lies in the molecular structure of the oat starch also seems weak. His has seen good effects from the use of oat extracts. It may be true that there is an extractive substance in oatmeal which stimulates the internal secretions of the pancreas.

The great variety in symptoms and severity as shown in diabetes in human beings demands many varieties of treatment. In all but the very mild cases the diabetic needs the constant supervision of his physician. Special care, however, must be taken when we wish to make diabetics with ketonuria sugar-free. The treatment of such patients in their homes is possible only if they are very intelligent, and it necessitates great firmness of character. In severe cases it is possible to make them sugar-free only in a hospital. Furthermore, in moderately severe cases a stay for a time in a hospital is advisable, particularly during any determination of the patient's degree of tolerance. A course of the waters at Carlsbad, Vichy, Neuenahr, Marienbad, Tarasp and other spas is often remarkably beneficial. The advantage of such a course is, according to von Noorden, shown by the fact that during it the patient can often be made sugar-free or can establish a high degree of tolerance on a less rigorous diet. In extremely severe cases the patients should not be sent to these resorts, but directly to a hospital. A very important element in the treatment is a liberal amount of carefully regulated exercise. Severely affected patients, however, must avoid overexertion, which often increases the glycosuria markedly, and may do actual harm.

Obese patients with a mild diabetes can, to advantage, be carefully treated for their obesity at the same time by restricting the number of calories in the diet; but, in severe cases, it is not advisable to attempt to reduce the body-weight. In cases in which gout is a complication, one must consider carefully the purin content of the diet.

Finally, in regard to the prognosis, the patient's age, environment and circumstances, and any complications, must be considered, as well as the severity of the glycosuria and ketonuria. I can not now go more into detail regarding prognosis, except to say that the occurrence of diabetes in early years does not preclude a complete cure. There are such patients who have been made sugar-free and have remained so, and are able again to follow their regular occupations. In these cases it is, however, always to be feared that, under unfavorable circumstances, such as excesses, overexertion or excitement, the sugar may reappear. In this connection the character of the patient is very important. Moderation, self-control and steadfastness are essential. I regard such patients as cured, although the predisposition to diabetes is still present. It is only in the same sense that we are able to consider a tuberculous patient cured.

# THE PRODUCTION OF MORBID CHANGES IN THE BLOOD VESSELS OF THE RABBIT BY ALCOHOL\*

## A PRELIMINARY REPORT

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### INTRODUCTION

The production of morbid changes in the lower animals by the use of drugs, various chemicals and, in some cases, by the employment of mechanical devices has opened an instructive field for medical investigation. The general aim of such investigation has been, first, to determine whether definite and fairly constant pathologic changes could be produced by the use of various agents, and, second, after this has been determined, to arrest or to modify these changes by the use of other agents of a remedial nature.

In recent years there has been developed an extensive literature through the work of various investigators on experimental arteriosclerosis. The contributions of Josué, Fischer, Kurt, Klotz, Miller<sup>1</sup> and others have demonstrated that degenerative arterial changes follow the intravenous injection of adrenalin, digitalin and diphtheria toxin. Boinet and Romany and Klotz, using the *Bacillus typhosus* and streptococcus, have with the same animals produced arterial changes primarily affecting the intima, which is greatly thickened by endothelial proliferation.

Klotz,<sup>2</sup> in an interesting series of experiments, in which rabbits were suspended by their hind legs, demonstrated a rise in arterial pressure by the mechanical aid of an excessive amount of blood in the aorta and forelegs. Five animals thus treated developed changes in the aorta, carotid, subclavian and brachial arteries. No changes were demonstrated in the control animals. It has also been shown by Klotz<sup>3</sup> that bacterial toxins are capable of producing changes in the intima of the aorta and pulmonary artery.

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\*From the Laboratory of Experimental Therapeutics of the University of Chicago, S. A. Matthews, M.D., Director.

1. Miller (J. L.): Spontaneous Arterial Degeneration in Rabbits. Jour. Am. Med. Assn., 1907, xlix, 1789.

2. Klotz: Centralbl. f. allg. Path. u. Physiol., 1908, xix, 535.

3. Klotz: Brit. Med. Jour., 1906, ii, 1767.



Undoubtedly spontaneous arterial disease occurs in the lower animals, and perhaps more frequently in the rabbit, for this animal is peculiarly susceptible to surroundings and changes which depart from the normal. The occurrence of spontaneous aortic disease in rabbits has been demonstrated by Wells and also by Amy B. Miles.<sup>4</sup> The probability that such changes are not very frequently encountered is, however, strengthened by the report of Pearce,<sup>5</sup> who examined sixty-two rabbits. Of these, fifty were normal rabbits. Vascular lesions were found in but three, and in each case consisted of a few minute patches of sclerosis at the beginning of the aorta. In the remaining eleven animals degenerative changes were found in the aortas of four. These were animals that had been subjected to the action of typhoid and other sera.

The object of the present investigation was to determine whether sclerotic changes could be produced in the vascular system of the rabbit by the use of alcohol.

#### METHOD OF ADMINISTRATION, DOSAGE AND THE IMMEDIATE EFFECT OF ALCOHOL

At the commencement of this series of experiments the alcohol in 30 per cent. solution was given intravenously. By such a method of administration, changes, if any should develop in the vessels, could be logically ascribed to the direct action of the alcohol, and thus there would be eliminated the many modifications to which the drug is subjected before it reaches the vessels when it is introduced into the stomach. The intravenous injections were, however, rapidly followed by the formation of thrombi in the neighboring vessels, necessitating the drug being given by the stomach. For this purpose a small, soft rubber catheter was used.

In each case for the first few days 25 c.c. of a 10 per cent. solution was given once a day. After this the quantity was increased to 50 c.c. and the strength of the solution to 20 per cent.

The immediate effect of the alcohol was greatly enhanced by this method of administration, the excitement being marked. In all the animals the respirations and heart were markedly accelerated. This condition usually lasted about an hour. Then the animal would become drowsy. At this stage voluntary movements were slow and all muscular acts imperfectly coordinated. Following an hour or more of drowsiness

4. Miles (Amy B.): Spontaneous Aortic Diseases in Rabbits. *Jour. Am. Med. Assn.*, Oct. 5, 1907, xlix, 1173.

5. Pearce (R. M.): Occurrence of Spontaneous Arterial Degeneration in the Rabbit. *Jour. Am. Med. Assn.*, 1908, li, 1056.

the animals would usually fall asleep for two to six hours. Their return to the normal was gradual, the effect of the alcohol lasting on an average of twelve hours.

GROSS AND MICROSCOPIC CHANGES PRODUCED IN THE VESSELS OF ANIMALS  
SUBJECTED TO THE ACTION OF ALCOHOL

In the following observations the aorta was the vessel selected for study in determining the presence or absence of sclerosis. The agents used were Zenker's fluid, hematoxylin and eosin:

*Experiment 1.*—The subject received 50 c.c. of 20 per cent. alcohol for thirty-four days. The aorta at its origin and for a distance of 1 c.c. was visibly thickened. Just at its commencement and situated so as to encroach on one of the coronary openings there was a nodule the size of a pin-head. The microscopic examination of the tissue taken from the thickened portion of the arch showed very clearly, when compared with sections of the thoracic portion of the aorta, a thickening of both the inner and middle coats of the vessel. This change in the internal coat was due to a proliferation of the connective-tissue cells in the subendothelial layers. In the media small round cells and fibroblasts were numerous between the muscle bundles. The muscular element was not degenerative. There had been no transition of the connective-tissue cells into true fibrous tissue. The change was an early one and apparently as extensive in one coat as in the other. The nodule referred to was situated in the intima and was formed principally of elongated cells, which stained poorly and had undergone a granular, non-fatty degeneration. There were no adjacent changes in the media.

*Experiment 2.*—The subject received 50 c.c. of 20 per cent. alcohol for forty days. The aorta showed no evidence of atheromatous changes. Sections through the vessel at various levels showed no evidence of disease.

*Experiment 3.*—The subject received 50 c.c. of 20 per cent. alcohol for 40 days. The thoracic aorta was the seat of a clearly defined atheromatous ulcer. Elsewhere the vessel was normal. The ulcer in the thoracic involved both the intima and media. Its floor was formed by the adventitia, and consisted of young connective tissue in the cellular and fibrous stages. Calcification was not present.

*Experiment 4.*—The subject received 50 c.c. of 20 per cent. alcohol for thirty days. The aorta was normal in structure.

*Experiment 5.*—The subject received 50 c.c. of 20 per cent. alcohol for twenty days. The animal was accidentally killed. The aorta presented no evidence of disease.

*Experiment 6.*—The subject received 50 c.c. of 20 per cent. alcohol for forty-two days. The aortic valves were thickened, and felt rough. The aorta showed two calcareous patches, one in the arch and one in the thoracic portion. There was a diffuse thickening of the inner and middle coats, the histologic appearance bearing a close resemblance to the changes seen in the aorta of the first animal. The areas of calcification occupied chiefly the intima, but extended also to the media, having ruptured the inner elastic lamina. Here it may be interesting to note that the hyperplastic changes which have been demonstrated in the inner coats of the aorta were not preceded by localized degeneration and weakening of the middle coat. The changes in the vessel were usually of a diffuse character. There was evidently no pronounced localization in the action of the substance or substances which induced changes in the vascular system from the continuous use of alcohol.

*Experiment 7.*—The subject received 50 c.c. of 20 per cent. alcohol for fifty days. The aorta showed an atheromatous ulcer 1 cm. from the aortic ring and a small warty growth on one of the aortic valves. The ulcer involved the intima and a portion of the media. The amount of cell infiltration in the media was less than in preceding cases.

*Experiment 8.*—The subject received 50 c.c. of 20 per cent. alcohol for forty-four days. There were no changes in the intima. Sections through the aorta at various levels frequently showed in the middle coat, between the muscle bundles, collections of small round cells. Other than this there was no evidence of connective-tissue overgrowth.

*Experiment 9.*—The subject received 50 c.c. of 20 per cent. alcohol for thirty-three days. The upper portion of the aorta showed several areas that were visibly and palpably thicker than the surrounding vessel. Sections through these areas showed the thickening to be due to a proliferation of the subendothelial connective tissue. The cells and nuclei stained well. There was no evidence from the staining reaction or from the size of the cells or their nuclei that the degenerative changes existed.

*Experiment 10.*—The subject received 50 c.c. of 20 per cent. alcohol for twenty-four days. The aorta was normal.

*Experiment 11.*—The subject received 50 c.c. of 20 per cent. alcohol for fifty days. The aorta showed a patch of thickening behind one of the semilunar valves and in the thoracic aorta there were several deep ulcers. Opposite the larger of the ulcers the vessel was bulged (early aneurism formation). This area measured 1 cm. in its longest diameter. The floors of the smaller ulcers, which were not so deep as the larger one, were found in the middle coat. The floors did not consist of the histologic elements of the media, but of young connective tissue fibers and spindle-shaped cells. This reparative fibrosis lessened as sections away from the ulcer were examined. It did not come to a clear-cut termination, but the marked localized connective tissue overgrowth existed to a less degree in a general thickening of the middle coat at some distance from the ulcers.

*Experiment 12.*—The subject received 50 c.c. of 20 per cent. alcohol for fifty-four days. The aorta was the seat of several areas of nodular sclerosis, the nodules being to a great extent confined to the intima, while the media presented the usual diffuse connective-tissue hyperplasia.

*Experiment 13.*—The subject received 50 c.c. of 20 per cent. alcohol for fifty-four days. There was diffuse cell infiltration of the middle coat.

#### A STUDY OF THE AORTAS OF PRESUMABLY NORMAL ANIMALS

The animals used as controls were all full grown; eight of the number were old. The aortas of the sixteen control animals were examined in the same way as the vessels of those animals subjected to the action of alcohol.

The following is a summary of the changes found:

In thirteen of the animals the aorta was free from both general and localized thickening. In the three remaining animals the vascular changes were as follows: In one aorta there was a sclerotic nodule in the arch; in the two remaining vessels atheromatous ulcers were found in the thoracic aorta. There was an absence of diffuse thickening, especially in the media. This observation naturally suggests that the etiologic factor in the development of the vascular changes in the control

animals was of a localized nature. The frequency with which diffuse changes are seen in the vessels of the alcoholic animals suggests some diffusely acting agent.

#### PRELIMINARY DEDUCTIONS

The number of animals used in these experiments is too small to permit the formulation of any permanent conclusions from the results. Definite sclerotic changes developed in the aorta in a decided majority of the animals that were subjected to the action of alcohol. Such was the case in nine of the thirteen animals used. These changes varied in intensity from a small round-cell infiltration of the media to the production of an atheromatous ulcer 1 cm. in its longest diameter. The most constant change was a diffuse thickening of the media. Similar changes were present in the vessels of relatively few normal animals. The changes which were present were localized and were not nearly so extensive as those seen in the vessels of the alcohol animals, even though the control animals were old, the other animals not being full grown.

A continued study of this subject will consist in the following measures: First, an attempt will be made to demonstrate morbid changes in the vessels of a larger series of animals. Second, if it can be definitely proved that such changes are produced fairly constantly by the use of alcohol, an endeavor will be made to determine whether the alcohol *per se* is capable of causing such results, or whether the changes arise indirectly by the action of alcohol inhibiting the activity of the various digestive enzymes and predisposing to or directly leading to some type of autointoxication.



## BOOK REVIEW

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PULMONARY TUBERCULOSIS AND ALL COMPLICATIONS. BY SHERMAN G. BONNEY, M.D., Professor of Medicine, Denver and Gross College of Medicine, Denver. Philadelphia and London: W. B. Saunders Company, 1908. Cloth, \$7.00 net; half morocco, \$8.50 net.

In the struggle against tuberculosis there are many indications that the lay public is getting enlightened more rapidly than the profession, and the one reason for this is probably the fact that a comprehensive book, dealing with all phases of the subject, was not accessible in English. Dr. Bonney has changed this state of affairs very much, for although he says in the preface that the work was not intended to be exhaustive, it is so nearly so that the title is somewhat misleading, and the descriptions of the localizations of tuberculosis outside of the lung are in many cases adequate for other than "complications" of pulmonary tuberculosis. The general plan is a good one and is well carried out. Historical review, biologic features of the bacillus tuberculosis, methods of infection, clinical phenomena, diagnosis and treatment, are all discussed in a manner that is almost always satisfactory, and never leaves out anything of importance. As examples of the author's views, already known to many readers, his opinion of the routes of infection is that both respiratory and digestive channels are involved according to opportunity, the former less frequently, the latter more, than has been believed; he is not enthusiastic regarding the diagnostic use of tuberculin, but his method of using it, and his interpretation of the results, are not like those of most others who have a different opinion; his experience with infection from aspiration of the pleural cavity seems rather more unfortunate than that of many others. For examples of excellent work one may point to the section on physical diagnosis, full of sound knowledge and a large experience well digested; or to that on prognosis; but many others are equally satisfactory and all deserve careful study. The book is profusely illustrated and most of the illustrations are very good. Some of the many roentgenograms, however, have suffered from the reproduction. The illustrations of hands are good, but seem less instructive than photographs. Most of the numerous case reports are instructive and well condensed, but one may question whether all the professional connections are essential. The chapters on the arrangement and location of institutions on "What the Public Should Know," the scope of sanatoria, climate

and treatment are all admirable, the remarks on treatment showing how one can be a wise therapist and still have certain doubts as to the finality of even the latest methods. In a book with so much in it it would be extraordinary to find no errors. Serious ones we have not found, but it should be pointed out that the principle of staining the tubercle bacillus is not, necessarily, to employ carbol fuchsin, but a basic dye. The language used is in general superior, not rarely suggesting Gibbon or Johnson. This makes all the more striking such an expression as "the la grippe influence" (p. 99). The author has good examples for translating "perl" into French, but the mongrel "perle disease" (p. 29) seems unnecessary. Sir Michael Foster hardly needs the reportorial predicate "renowned." Some of the proper names have suffered at the hands of the proof-reader; "Silician" for "Silesian" (p. 625) may be mentioned. On the whole, the volume is an important addition to medical literature, and a timely one, and a wide reading and study of it should add much to the organized combat against tuberculosis. The publisher has done his work well.

# SARCOSPORIDIOSIS

WITH REPORT OF A CASE IN MAN

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## INTRODUCTION

The members of the class sporozoa, known as sarcosporidia, while commonly found in several of the domestic animals, are very rarely encountered in man; so rarely, indeed, that from a search through the literature available here in Panama it would seem that this report of the presence of *Sarcocystis sp. inc.* in the striated muscle fibers of man is the third positive one in the literature. The case presented here is of additional interest because of the fact that the parasites were discovered in their living host and removed on two occasions, that they disappeared from the tissues within a period of four months, and that the host is living and well and still under observation.

Sarcosporidia are oval, cylindrical or fusiform bodies found either within or between the striated muscle fibers of various representatives of mammalia and reptilia. They may be extremely small and microscopic or as long as a muscle fiber and quite visible to the naked eye. They have various breadths. The smaller forms are generally found within the muscle fibers, while the larger forms may distend the muscle fibers to several times their normal diameter. Smaller and larger forms are found at times outside the muscle fibers in the connective tissue spaces of the endomysium. In these locations the sporozoa may grow to considerable size. The youngest sarcosporidia observed of the species *Sarcocystis muris* are 15 microns in diameter and consist of a collection of small spherical bodies, each having a central nucleus. The collection of spherical bodies or this polynucleated body is enclosed within a thin refractile capsule. The sporozoön increases in size by a multiplication of its nuclei; vesicular cells (sporoblasts) are formed, which are arranged in groups or chambers. By a final division of the nuclei of these sporoblasts in the chambers, oval, crescent or banana-shaped sporozoites are formed. The sporozoites contain each a nucleus, chromatoid granules, a few minute vacuoles and, according to some observers, a polar capsule and a polar filament. In *Sarcocystis muris* the chromatoid granules are frequently heaped up in one end of the sporozoites and might easily be called polar capsules. Mature sporozoites recently removed from their



host and suspended in saline solution at room temperature, 74 to 86 degrees F., are seen to have a peculiar slow motion along the line of their projected curvature and also around their long axis—a very slow, interrupted, gyratory and spiral motion, which has been well described by Theobald Smith. Flagella could not be demonstrated by the *intra vitam* gentian violet or methylene blue staining methods, which usually bring out the cilia and flagella of protozoa beautifully.

### HISTORICAL

The discovery of sporozoa, parasitic in striated muscle, was made by Miescher<sup>1</sup> in 1843, who described milk-white filaments in the striated muscles of domestic mice. The filaments were visible to the naked eye and ran parallel with the muscle fibers; they were cylindrical tubes, containing innumerable elongated or kidney-shaped and a smaller number of globular forms. This observation of Miescher was verified by Hessling,<sup>2</sup> who found "Miescher's tubes" in the striated muscle of deer, cattle and sheep. G. Rainey<sup>3</sup> in 1858 published an account of the development of what he believed to be *Cysticercus cellulosæ* in the muscles of the pig; what Rainey really described was the Miescher tubes of the sarcosporidial disease of pigs. Rainey's error was corrected by Leuckart<sup>4</sup> in 1863. Soon after this Manz<sup>5</sup> attempted the infection of guinea-pigs, rats and mice by the parasites which he found in rabbits.

Braun<sup>6</sup> mentions that sarcosporidia had been found in domestic fowl by J. Kuhn<sup>7</sup> in 1865. Rivolta, Riley, Belagér, Leidy and Barrows observed the parasitism of sarcosporidia in birds. Three sarcosporidia found in ducks and a grosbeak were described by Stiles<sup>8</sup> in 1893.

According to Wasielewski,<sup>9</sup> sarcosporidia have been found in the muscle fibers of *Bos taurus*, *Bos bubalus*, *Canis familiaris*, *Capra hircus*, *Cervus capreolus*, *Cervus elaphus*, *Equus caballus*, *Felis domestica*,

1. Miescher (F.): Ueber eigenthümlichen Schläuche in der Muskel, einer Hausmaus. Ber. ü. d. Verhandl. d. naturf. Gesellsch. Basel, 1843, v, 198.

2. Hessling: Histologische Mittheilungen. Ztschr. f. wissenschaft. Zool., 1854, v. 189.

3. Rainey (G.): Structure and Development of *Cysticercus Cellulosæ* as Found in the Muscles of the Pig. Tr. Roy. Phil. Soc., 1858, cxlvii. 3.

4. Leuckart (R.): Die Menschliche Parasiten, ed. 1, 1863, 1, 237.

5. Manz (W.): Beitr. z. Kenntniss des Miescherchen Schlauch. Arch. f. mikr. Anat., 1867, iii, 345.

6. Braun (Max): The Animal Parasites of Man, New York, 1906.

7. Kuhn (J.): Mitth. u. d. landwirtsch. Inst. zu Halle, 1865, p. 68.

8. Stiles: Notes on Parasites, Bull. 3, Dept. Agric., Bureau of Animal Industry, 1903.

9. Von Wasielewski: Sporozoenkunde, Jena, Gustav Fischer, 1896.

*Homo sapiens*, *Inuus species ape*, *Lepus cuniculus*, *Lepus timidus*, *Macropus penicillatus*, *Mus musculus*, *Mus rattus*, *Otaria californica*, *Ovis aries*, *Sus domestica*, *Sus larvatus*, *Sus scrofa*, *Anas boschas*, *Corvus sp. inc.*, *Gallus*, *Habia ludoviciana*, *Parula pidiaymi*, *Spatula clypeata*, *Turdus merula*, and *Platydictylus facetanus*.

Representatives of the sporozoa exhibit particular host relationships. They are peculiarly specialized parasites and select their hosts on account of affinities unknown to us. On this account the parasitism of certain species of sarcosporidia may be limited to particular hosts, or the phases of development and the morphology of a species may become so altered in an unusual host that the parasite could not be specifically identified. The natural mode of infection by sarcosporidia is unknown. Kasperek<sup>10</sup> was unsuccessful in his attempt to infect white mice and guinea-pigs with the sarcosporidia of sheep. Theobald Smith,<sup>11</sup> in a series of convincing experiments, demonstrated that gray and white mice might become infected with *Sarcocystis muris* by eating flesh from infected mice containing ripe mobile sporozoites. The muscle fibers became invaded so as to be recognized after the forty-fifth day. The ripened sporozoön in the mouse was found two and one-half to three months after the date of feeding. In rats I have noticed that invaded muscle fibers and the perimysium and endomysium showed no changes referable to the sarcosporidial infection. Muscle cells containing young parasites stained exactly like unaffected fibers near by. The life of the parasite within the tissues of the rat is undoubtedly a long one; the sporozoön slowly increases in size, ultimately outgrows in breadth the muscle fiber and may die within its host and be removed by phagocytes. Negri<sup>12</sup> has recently infected guinea-pigs by feeding them with the flesh of rats infected with *Sarcocystis muris*.

In Braun's opinion, there have been two undoubted cases of infection in man by sarcosporidia. The first case was reported by Kartulis,<sup>13</sup> who observed Miescher's cylinders of various sizes in the liver (?) and in the muscular system, but not in the fibers, of a Soudanese who had succumbed to multiple abscesses of the liver and abdominal muscles. Doflein<sup>14</sup> regards this case as doubtful. There can be no doubt, however, about the case reported by Baraban and St. Remy<sup>15</sup> in 1894. These

10. Kasperek: Centralbl. f. Bakteriöl., 1895, xviii, 327.

11. Smith (Theobald): Jour. Exper. Med., 1901, v; 1902, vi, 303.

12. Negri (A.): Beobachtungen über Sarkosporidien, Centralbl. f. Bakteriöl., 1908, xlvii, 612.

13. Kartulis: Ueber pathogenen Protozoen bei Menschen. Ztschr. f. Hyg. u. Infektionskrankh., 1893, xiii, 1.

14. Doflein: Die Protozoen. Jena. 1901. Gustav Fischer.

observers found sarcosporidia distending the muscle fibers to four times their normal thickness in the laryngeal muscles of a man who had been executed by hanging. The sporozoön was 1.6 mm. long and 0.17 mm. thick with a thin capsule. The spores were banana-shaped and were 8 to 9 microns long. All individuals were in the same stage of development and the sporoblasts developed in room systems. Lindemann<sup>16</sup> in 1868 described some brownish masses found on the heart valves and in the myocardium of a person who had died of dropsy. The bodies were 3 mm. in length and 1.5 mm. in breadth and were regarded by Lindemann as gregarines. Rosenberg<sup>17</sup> found numerous small encysted refractile bodies in a papillary muscle of the mitral valve. The cyst was 5 by 2 mm. and contained no hooklets. The exact nature of the bodies in these two latter cases was never determined.

It is remarkable the sarcosporidia infections are not more common in man, especially when we recall the high percentage of infected domestic animals—sheep, 95 per cent., and pigs, 98.5 per cent. It must be borne in mind, however, that several of the species of sarcocystis are extremely minute, and that, as Theobald Smith says, "the muscular system in man is not subjected to that scrutiny which the viscera undergo in pathologic inquiries, and that sarcosporidia may be present and yet not be recognized." Sarcosporidia may be overlooked very easily by careful observers, probably on account of their resemblance to tendon, nerves and streaks of fascia. In a recent account<sup>18</sup> of the pathologic conditions found in plague rats in San Francisco no mention was made of the presence of sarcosporidia in the rats examined, although they must have been present in some of the 50,000 rats examined during the four months.

#### REPORT OF A CASE IN MAN

*Patient.*—J. H., negro, aged 20, native of Grace Church Parish, Barbados, arrived on the Isthmus of Panama, Jan. 10, 1908, and went immediately from Colon to Gatun,<sup>19</sup> remaining there one and a half days; thence to Empire,<sup>20</sup> where he rented a room from his brother and took some of his meals with the latter. Most of his food was obtained from the commission camp at Lirio.<sup>20</sup> His meals on Sunday were taken with his brother. The diet was bread and tea, canned fish boiled with vegetables, pigtail boiled with rice, fowl fried or stewed. All food was cooked

15. Baraban and St. Remy: Compt. rend. Soc. biol., Paris, 1894, x, 201.

16. Lindemann: Ueber der hygienischen Bedeutung der Gregarinen. Deutsch. Ztschr. f. Staatsarzneikunde, 1868.

17. Rosenberg: Ein Befund von Psorospor. in Herzmuskel des Menschen. Ztschr. f. Hyg., 1892, xli, Page 435.

18. McCoy (G. W.): Pathological conditions found in rats—Observations based upon examination of 50,000 rats in the laboratory of the Public Health and Marine Hospital Service, San Francisco, Calif. Pub. Health Rep., 1908, xxiii, No. 39.

except mangoes and other fruit. Drinking water used at this time by the patient was that from the municipal supply. At one period the patient was employed as a track-layer in the canal prism and drank any water at hand. Some time before his present illness he was admitted to Culebra<sup>19</sup> hospital with fever (slight attack) and discharged after two and a half days. About May 15 the patient went to work for the Panama Railroad, living in a ear, dieting himself, drinking water wherever he might be, using "spring" water or that from the municipal taps between La Casetas<sup>19</sup> and Tabernilla.<sup>19</sup>

*Illness.*—This began about June 10 with fever, slight headache and stiffness of the muscles and joints. The patient was admitted to Ancon<sup>19</sup> Hospital June 10, complaining of fever, pain in body, vomiting and headache. On examination, his abdomen, liver and spleen were found to be negative; there was some blowing breathing in the right base posteriorly. The following day he complained of pain in his joints.

*Clinical Findings (by weeks).*—First week (June 12-18): Temperature irregularly continuous, 100 to 103.5. Blood culture sterile: June 17, bile glycerin media; probably an insufficient amount of blood was collected, the patient being delirious. Widal test, June 16, negative. Leucocytes, June 12, 5,400; June 15, 9,800; June 17, 16,000. Pain in joints. Patient constipated.

Second week (June 19-25): Temperature irregularly continuous, 99.8 to 102.5. Patient delirious, noisy and restless; slept very little. Pain in back. Patient complained of "cutting" in the bowels. Three Widal tests, June 20, 22 and 24, negative.

Third week (June 26-July 2): Temperature irregularly continuous, 98.8 to 101.3. Patient delirious and noisy; constipated. Stool negative for tubercle bacillus. Widal test, June 26, negative. Leucocytes, June 26, 15,600. Differential count: Polymorphonuclears, 55 per cent.; small mononuclears, 25 per cent.; large mononuclears, 14 per cent.; transitionals, 6 per cent.

Fourth week (July 4-9): Temperature remittent, 98 to 101.5 first three days, later becoming continuous, 99 to 100. Patient complained of cramps in abdomen, pain in right side; constipated. Widal test, negative. Red blood corpuscles, 5,336,000. Ocular tuberculin reaction, negative. Piece of tissue removed from right arm for diagnosis, to be examined for trichina at request of Dr. Bates. Widal test, July 4, negative; July 9, positive. Urine: Phosphaturia present, diazo reaction positive. Stool, negative. Emaciation present; no muscle tenderness.

Fifth week (July 10-15): Temperature slightly remittent, 98 to 100. Widal test, July 10, positive; July 13, negative, suspicious. Patient propped up in bed. Piece of tissue removed from right arm for examination.

Sixth week (June 17-23): Temperature, 98 to 100.5.

Seventh week (July 24-30): Temperature, 98 to 100. Leucocytes, July 25, 12,100. Differential count: Polymorphonuclears, 58.5 per cent.; large mononuclears, 11 per cent.; small mononuclears, 25 per cent.; eosinophiles, 3 per cent.; transitionals, 1.5 per cent.; mast cells, 1 per cent.

Eighth to twelfth week (July 31-Aug. 31): Temperature normal. Patient gaining in flesh and strength. August 6, leucocytes, 8,500; red blood corpuscles, 5,216,000. Differential count: Polymorphonuclears, 39 per cent.; large mononuclears, 8.5 per cent.; small mononuclears, 42.5 per cent.; intermediate mononuclears, 4.5 per cent.; transitionals, 2.5 per cent.; eosinophiles, 2.5 per cent.; mast cells, 0.5 per cent.

On the patient's recovery and discharge from the hospital he was given employment at the laboratory, where he could be kept under observation. It was noticed that his vision was defective, and on September 2 he was referred to Dr. Lyster for examination, who reported as follows:

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19. Villages in the Canal Zone.

Retinoscope: + 1.50 right; + 1.50 left. Vision: Right, 20/100; left, 20/100. Right eye: One vein tortuous, nerve small but distinct, arteries smaller than normal. Left eye: Nerve outline lost, lower half of retina atrophic, veins interrupted by blank spaces, arteries very small, veins full and tortuous.

On September 24 he complained of a "cutting" in the bowels. The stools at this time contained no typhoid bacilli. There was some mucus, pus cells, numerous yeast cells and a few trichomonas signets.

October 1: The patient had improved in health and appeared normal.

*Histologic Examination.*—Tissue from left biceps, obtained July 3: A small piece (about 4 mm.) of the left biceps was removed under cocaine, fixed in Zenker's solution and paraffin sections were stained with eosin and hematoxylin. There was some distortion of the fibers, probably due to the removal of such a small bit of tissue. Here and there were oval or round dotted bodies about the width of a striated muscle fiber, their length being about twice that. The muscle fiber was not distended by the presence of the dotted body. One oval body measured 0.084 mm. in length and 0.027 mm. in width. One of the bodies in cross section was circular and was 0.021 mm. in diameter. The oval or round bodies were strongly contrasted from the eosin-staining muscle fiber by the very pronounced blue stippling of the former. This stippling was seen under the high power to be due to the nuclei of small oval sporozoites. In this section there was some hyaline change in the muscle fibers, both in the infected and the non-infected fibers. Occasionally within the capillaries near one of the oval bodies there was a slight increase in the number of polymorphonuclear leucocytes and there were a few foci of acute myositis involving a single fiber. Some of the specimens showed a cross-section of the sporozoön, in which it was seen that the latter was just within the sarcolemma. No matter how wrinkled or distorted the muscle fiber might be, the sporozoön, with its very thin refractile membrane, was seen to preserve its circular or oval outline. Under the highest powers the sporozoön was seen to be made up of hundreds of little oval vesicular bodies having a round nucleus at one end. The sporozoite took the eosin irregularly and appeared to be vacuolated. The little sporozoites were decidedly vesicular and were either round or oval. All had one nucleus and very rarely two nuclei placed at opposite ends of the short axis of the sporozoite. The sporozoites were closely packed within the mother capsule or membrane, yet without any arrangement suggesting a room system. The measurement of sporozoites in the section was: length 4.25 microns, width 1.75 microns.

Tissue from right arm, obtained July 13: Ten days after the first examination another small piece of muscle was removed, this time from the opposite arm. The muscle fibers were pale and apparently edematous and turbid. There were no gross evidences of sarcosporidia. This section showed an extensive destruction of the muscle fibers and a slight invasion of the same by the sarcosporidia. The destruction of muscle fibers amounted in different fibers from 50 to 75 per cent. of the whole number. The degenerated fibers stained faintly with eosin and consisted of a fine granular material resembling coagulated serum. The degenerative process appeared to start oftencst in the center of a fiber, extending concentrically or eccentrically toward the periphery. The sarcolemma remained intact. In some of the fibers, where foci of necrosis had appeared, there were some large round and oval bodies resembling phagocytes, their nuclei alone being visible; the cytoplasm remaining hidden. Occasionally a channel had been cut into the center of the fiber by polymorphonuclear and mononuclear phagocytes. In places the muscle had undergone a hyaline liquefactive necrosis, which began in that part of the fiber just beneath the sarcolemma. In other places the degeneration of the fiber occurred by a process of fragmentation of the individual muscle into fibrillar blocks. The necrosis and myositis were greatly out of pro-

portion to the number of sporozoa present. Some of the muscle fibers had been replaced completely by plugs of polymorphonuclear and mononuclear cells, but in these fibers or within these areas no sporozoa could be detected. In this section the sporozoa were apparently of two ages: (a) very few small younger bodies crowded with hematoxylin-staining sporozoites; (b) older amebiform (in cross-section) sporozoa within a muscle fiber which had lost its cytoplasm. These latter did not contain so many sporozoites; some had escaped and lay just without the membrane of the sporozoön and within the sarcolemma of the muscle fiber. These sporozoites were elongated, sickle-shaped and nucleated, with eosin-staining cytoplasm.

Tissue from right biceps, obtained July 13: A piece of tissue was macerated in sterile saline solution at room temperature for fifteen days for further possible development of sporozoites. Sections of this tissue did not stain well and there was no further developmental change in the sporozoön or its sporozoites. Examination of teased fresh tissue from the right biceps and from tissue incubated for fifteen days in sterile saline solution showed numerous oval slightly refractile sporozoites with eccentrically placed nuclei. Stained with Leishman's or Hasting's stain the sporozoites appeared larger than in sections, but their morphology was the same.

Tissue from right biceps, obtained November 8: Muscle taken after the patient had been at work in the laboratory for several weeks. The arm was plump and the subcutaneous fat was increased in amount. The muscle fibers, however, were rather pale and not of the normal color. Many sections from this tissue were examined but no parasites could be found. Here and there were collections of large and small connective-tissue cells in the endomysial spaces, probably representing the areas of necrosis noted on the previous examination. Quite a number of muscle fibers still showed hyaline necrotic spots either in their interiors or on the periphery of the fibers beneath the sarcolemma. These areas were met singly or in collections of three or four fibers.

#### INCIDENCE OF SARCOCYSTIS MURIS IN PANAMA

For the purpose of comparative study, an examination of some of the rats and mice and other animals caught near the city of Panama during the months of September and October, 1908, has been made.<sup>20</sup> Bats, lizards, calves and mice (*Mus musculus*) have failed to reveal an infection either to gross or microscopic examination. Nearly 2,000 rats have been examined. It was noticed early in the course of examination that the immature rats were not visibly infected. In some instances house infections were noticed; cages of rats caught in one house would contain three or four infected rats, while several other cages from other localities, containing 30 or 40 rats, would have no infected animal.

Of 131 adult rats examined grossly, 15, or 11.4 per cent., were infected. Of 89 young and half-grown rats, none was found to be infected grossly. Of 28 adult rats (*Mus rattus*) examined grossly, 2, or 3.5 per cent., were infected. Of 65 adult rats (*Mus decumanus*) exam-

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20. The biceps and diaphragm of the patients coming to autopsy are being examined microscopically for the presence of sarcosporidia, but none has been found in twenty-five cadavers.

ined grossly, 7, or 10.7 per cent., were infected. Of 324 rats of both species and all ages examined grossly, 22, or 6.7 per cent., were infected. Of 26 rats which apparently were not infected, 2 showed young sarcosporidia on microscopic examination. These were about the diameter of a muscle fiber or smaller, but, as they were located in the center of the fiber surrounded by muscle substance and were so minute (24 microns in diameter), they were not visible to the naked eye. Fetal rats and those newly born were not infected to gross examination.

	Size of Ripe Parasites.		Pan-sporoblasts.	Room Chamber, (Kammerung.)	Cuticle, Striated.	Sporozoite.	
	Width mm.	Length mm.				Width mm.	Length mm.
<i>Sarcocystis muris</i> . . . . .	.203*	13.	Yes.	Yes.	No.	.006	.012
<i>Mus decumanus, rattus.</i> <i>Mus musculus.</i>							
<i>Sarcocystis miescheriana</i> ..	3.	.5-4.	.005-.006	Yes.	Yes.	?	?
Swine, 98.5 per cent.							
<i>Sarcocystis bertrami</i> .. . . .		9-10.	.006	Yes.	Yes.	?	?
Horse.							
<i>Sarcocystis tenella</i> . . . . .		.04-20.	.005	Yes.	Yes.	?	?
Sheep, 98 per cent.							
<i>Sarcocystis blanchardi</i> . . .	?	?	?	Yes.	?	?	?
Cattle and buffalo.							
<i>Sarcocystis hueti</i> . . . . .	.02-.03	.3-4.	?	Yes.	?	.004	?
Seadog.							
<i>Sarcocystis platydactyli</i> ..	.4-2.	?	?	Yes.	?	.001	.003-.004
<i>Sarcocystis muris</i> . . . . .	.03	.1	?	?	No.		
From guinea-pig (Negri).							
<i>Sarcocystis lindemanni</i> . . .	.17	1.6	?	Yes.	No.†	. . .	.008-.009
Man (Baraban and St. Remy).							
<i>Sarcocystis sp. inc.</i> . . . . .	.027	.084	?	No.	No.	.00175	.00425
Writer's case.							

\* Fresh specimen.

† Striated according to Doflein.

The mature sarcosporidia in rats are visible as white streaks in the muscle fibers running parallel with them; their ends are attenuated and are easily seen unless deep in the fibers, but are no doubt often regarded as fascia or tendon and their real significance overlooked. Among some of the older rats the mature parasites will be seen to extend nearly the entire length of the muscle fiber. Several parasites in the recent state were measured and found to be 12 to 14 mm. in length and 0.2 mm. in width. One sporozoön in a section of muscle was 1.088 mm. long and

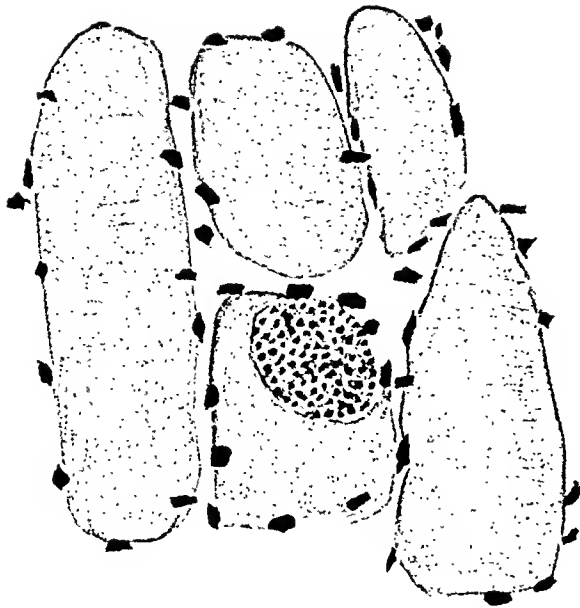


Fig. 1.—*Sarcocystis* sp. *hominis*. Oblique section of left biceps. Diameter of sporozoön, 0.045 mm.

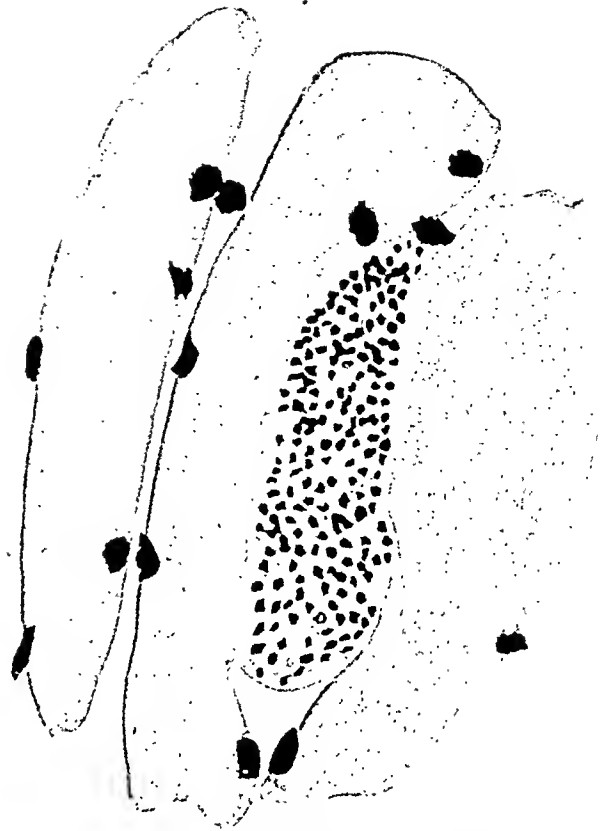


Fig. 2.—*Sarcocystis* sp. *hominis*. Section of left biceps. Length of sporozoön, 0.068 mm.; width, 0.021 mm.



Fig. 3.—*Sarcocystis* sp. *hominis*.  $\times 1,000$ . Section of right biceps ten days later than Figs. 1, and 2, showing sporozoön, ameboid in cross-section, occupying degenerated muscle fiber with leucocytosis, necrosis, myositis and phagocytosis. Some of the sporozoites have escaped from the sporozoön.







Fig. 4.—*Sarcocystis sp. hominis*,  $\times 4,000$ . Sporozoites from section of left biceps, showing earlier oval form. One of the sporozoites has two nuclei at opposite ends of the short axis.

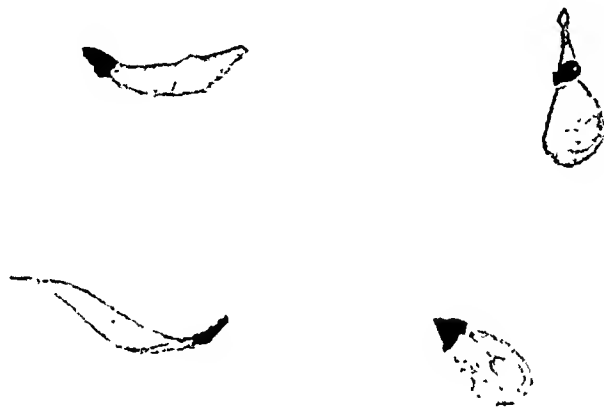
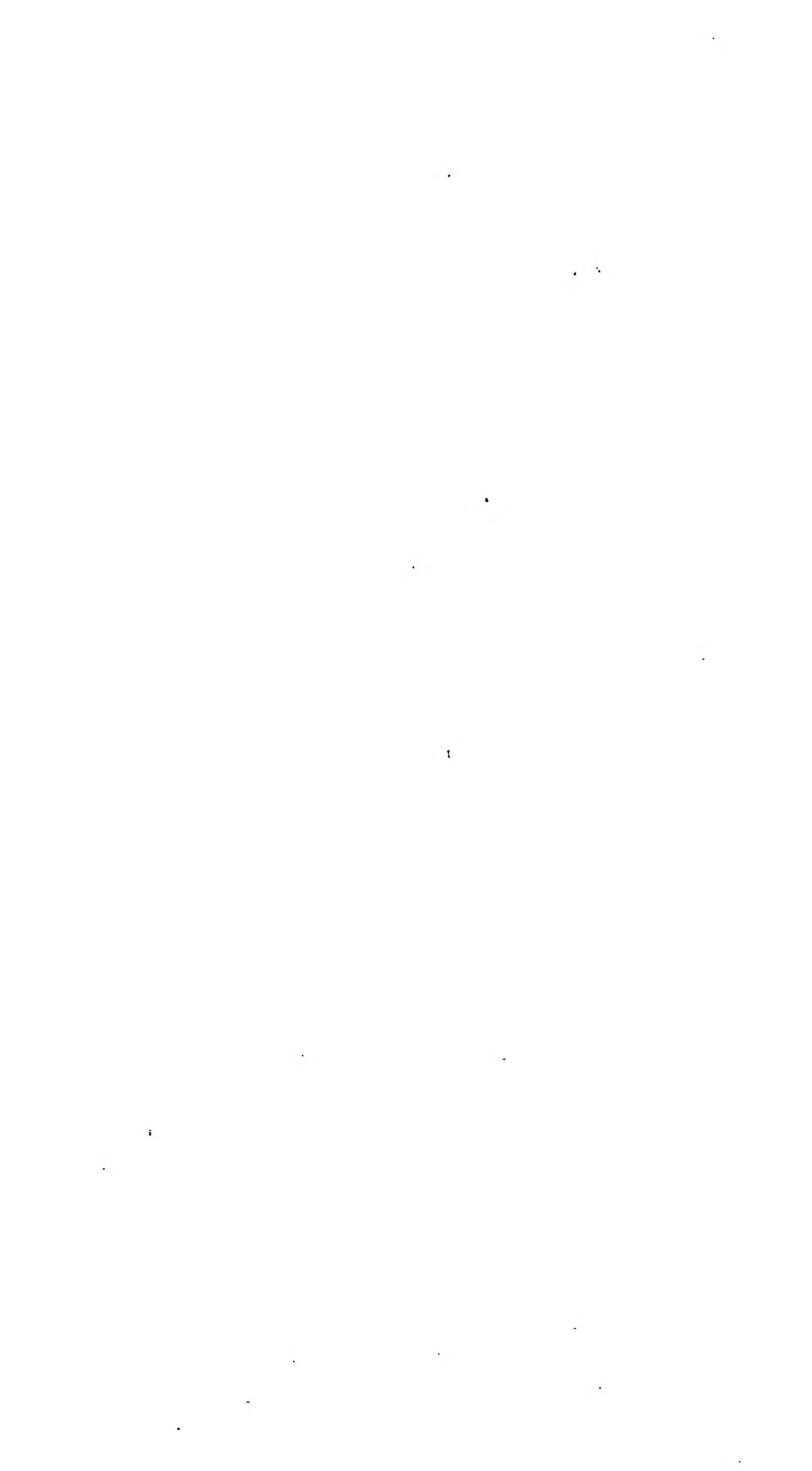


Fig. 5.—*Sarcocystis sp. hominis*. Sporozoites from section of right biceps taken ten days later than Fig. 4. The sporozoites have become attenuated and less vesicular; their nuclei elongate, and their cytoplasm shows an affinity for eosin.



Fig. 6.—*Sarcocystis muris*. Smear from ripe parasites taken from *Mus decumanus* (Hastings' stain), showing chromatoid granules suggesting a polar capsule, nucleus and polar vacuoles. Length, 0.012 mm.; width, 0.006 mm.; diameter of nucleus, 0.004 mm.



0.16 mm. wide. The sporozoa are tough, and with moderate care may be torn out of the muscle fibers in teasing without breaking their continuity. Although the capsule of a sareocystis is thin, the parasite is very resistant to pressure and, on crushing it with a cover-slip, it is seen that the sporoblasts are arranged in spherical collections or room systems. The older rats, as stated above, are more often infected than the younger ones. A moderate infection is one in which twenty to forty parasites may be seen in the superficial fibers of the animal. One rat (*Mus decumanus*) caught recently presented an extraordinary appearance, for each muscle had been largely replaced by parasites. The color of the muscle was reddish yellow and it was marked out by thousands of white lines or stripes running parallel to the entire length of each muscle. The rat was plump and well nourished, as all the infected rats were. and from a comparative observation made on the habits of caged wild rats he must have been a king of cannibals—a sort of “O, I am the cook, and the captain bold, and the mate of the Naney brig.”

The descriptions and measurements of the various species of sareocystis in the literature at hand are incomplete, so that it is impossible to tabulate synoptically the different species for the purpose of accurate analysis or classification, but the accompanying table gives one an idea as to some of the characters of members of this genus.

## SUMMARY

This case is one of sareosporidiosis occurring in a negro who passed through an attack of typhoid fever in which there was associated as a complication neerosis and myositis of some of the striated muscles.

Sareosporidiosis in man is probably an extremely rare condition and no doubt represents a chance infection by one of the sarcosporidia whose normal or customary habitat is some one of the domestic animals or still lower order of life. The sporozoa have disappeared from the muscle fibers of the patient; this was probably taking place July 13, when it was observed that the sporozoites were escaping from their capsule.

The sporozoön differs in several ways from the one described by Baraban and St. Remy. The latter is larger. It distends the fibers and its cuticle is striated. The sporozoite is longer. The sporozoön described here, however, is smaller and does not distend the fiber; its cuticle is not striated and the sporozoite is very small. The parasite described here is apparently abortive and does not develop room systems such as are figured in the case of Baraban and St. Remy. Nothing is known about the natural mode of infection, though from the experi-

ments of Theobald Smith and Negri it is most likely through the gastrointestinal tract.

Sarcosporidial infections appear to give rise to little or no discomfort.

The pains in the muscles and joints complained of were probably due to the necrosis and myositis of the muscle fibers caused by the typhoid bacillus and not by the presence of the sarcocystis or its toxin.

The blood changes were those of typhoid fever, in which during the period of myositis there was a leucocytosis. There was no eosinophilia, as in trichinosis. The ocular defects in this case are probably referable to the typhoid fever rather than to sarcosporidia.

I wish to express my thanks to Major J. L. Phillips, U. S. A., Superintendent of Ancon Hospital, for his kind permission to publish this account, and to Dr. J. P. Bates, in whose care the patient was, for calling my attention to the case and suggesting an examination of the muscle.

Ancon Hospital.

# PURPURA FULMINANS

CHARLES A. ELLIOTT, M.D.

CHICAGO

Cases of purpura fulminans have been so rarely reported and so little is known as to its clinical manifestations and causation that I feel no hesitation in publishing an account of the following case, especially since the general question of hemolysis is at present attracting so much attention, and the etiologic factor back of this unusual affection appears to be one of hemolytic nature.

## CASE HISTORY

*Patient.*—Helen M., aged 8 years, 7 months. Mother and father living and well. No brothers or sisters. One uncle died of tuberculosis of the lungs. Otherwise the family history is negative. No history of purpura or of "bleeders" in the family.

*Previous Illnesses.*—The patient had whooping cough at 3; she was sick two months; measles and chickenpox in her seventh year, both light attacks. She was never a robust child, but was always healthy, aside from the above acute infections, with a good appetite, and always in a state of fair nourishment.

*Present Illness.*—On May 3, 1908, she was taken sick with scarlet fever, her case being the only fatal one of sixty cases of scarlet fever at the Chicago Orphan Asylum during March, April and May, 1908. Hers was a "mild" attack, with fever above 102 for but one day, and a typical exanthem that rapidly faded. The angina was moderate and the cervical glands were but slightly enlarged. The patient was kept in bed four days after the temperature became normal, and at the end of this time her physical condition was good, desquamation was in progress, and the urine was free from albumin and casts. Ten days later the patient, being seemingly well, was allowed to go outdoors and play in a protected garden on warm afternoons.

May 20: Seventeen days following the onset of the scarlet fever the patient complained of sore throat, and the tonsils and cervical glands were found to be swollen. Otherwise the physical condition seemed normal, except for some desquamation on the chest and extremities.

May 21: The cervical glands were painful and much larger. The pharynx was red, and the tonsils were enlarged, but presented no ulceration or membrane. The heart showed a systolic murmur at the base. The urine contained albumin and a few granular casts. The temperature was from 102 to 104; pulse, 90; respirations, 26.

May 22: The cervical glands were not so large nor so painful. The temperature was 102; pulse, 82; respirations, 24. In the evening a purpuric spot, the size of a small coin, was noted on the inner aspect of the right ankle.

May 23: The cervical glands were markedly less swollen. The purpuric spot on the right ankle was one by two inches in diameter in the morning, but spread rapidly during the day until it covered most of the dorsum of the foot by night. A similar purpuric spot was noted on the left ankle, which rapidly spread. Fine petechial spots, the largest not larger than pin-heads, were seen scattered over the thighs, especially about the knees. The patient complained of

pain and burning in both feet, could not sleep, and was delirious at times. Temperature was 102; pulse, 106; respirations, 26.

May 24: The purpuric areas had extended to cover most of the dorsal and plantar surfaces of both feet, as far as the middle of the arches, except for the outer two toes of the left foot, which remained free. Large blebs were present on the dorsal surface of both feet. The affected toes were cold to the touch, and were evidently gangrenous. Purpuric areas appeared on the left hip, on the inner aspect of both wrists, and on the outer aspect of the left arm. A systolic murmur was heard over the apex as well as over the base of the heart. The second pulmonic sound was not accentuated. The lungs were resonant throughout, and no râles were heard. The spleen was not palpable. The abdomen showed nothing abnormal. The patient complained of a severe burning pain in the feet, and had frequent desire to urinate. The temperature was 102; pulse, 120; respirations, 26. The urine contained macroscopic blood; was of a bright cherry-red color, with but little sediment; specific gravity, 1008; acid, large amount of albumin; no sugar; microscopically many red blood cells, and a few granular casts, but no crystals or pus.

May 25: The patient appeared very anemic; in marked contrast to the appearance of the day before, the lips, face and hands were blanched. Gangrene of the toes and skin of the feet to the plantar arch was complete, except for the outer two toes of the left foot. Large blebs were present on the dorsal surface of both feet. The right leg showed a broad streak of discoloration (hematoxylin color) running from the dorsum of the foot to the inner aspect of the knee. There was a fine, light green line tracing the edge of this area. Similar hematoxylin-colored areas were present on the outer aspect of the left knee, at the base of the right thumb, on the left forearm, on the inner aspect of the thighs, and on the left patella. A very large hematoxylin-colored area was found covering the lower back, as high as the first lumbar vertebra, and extending around the left iliac region into the left groin. This area showed marked edema, and was painful on pressure, but the skin was smooth and there were no blebs present here. Many fine petechial spots, the largest not larger than pin-heads, were seen in the skin of both legs, especially about the knees. There was no evidence of deep hemorrhages into the muscles. The gums were not swollen or tender. The cervical glands were markedly smaller than on May 21. The patient had nose bleed, vomited, and had constant desire to urinate, passing a bloody urine. Temperature was 102; pulse, 130; respirations, 26.

*Blood Examination.*—Hemoglobin, 55-60 per cent.; red blood corpuscles, 2,720,000; white blood corpuscles, 65,400. Differential count (1,000 cells counted): Polymorphonuclears, 794; lymphocytes, 132, myelocytes, 52; large mononuclears, 16; eosins (polymorph.), 5; mast cell (polymorph.), 1. Three normoblasts were found in counting the above. Blood platelets were not found to be increased in numbers.

The needle-prick from which the blood was taken for examination continued to bleed for three hours, until death took place at 2:30 p. m., sixty-eight hours following the first appearance of purpura, and twenty-two days following the onset of scarlet fever.

*Autopsy.*—(Dr. A. A. Goldsmith and N. E. Wayson.) General aspect of body. Three hours postmortem. Body of a female child, 53½ inches in length. Postmortem rigidity fairly well marked in the extremities and neck. Moderate postmortem lividity. No putrefaction. Corneæ opaque. Lips pale, with a tinge of cyanosis.

Distribution of purpuric spots: Numerous areas of discoloration, of varying size and outline, and of uniform hematoxylin color, were seen scattered over the body surface. They were well outlined, and slightly raised above the surface, the larger areas being distinctly edematous. The distribution of these areas was

extensive, and they varied much in size (as seen by the accompanying illustrations). In general, they were more or less symmetrical, and appeared with more frequency and to greater extent, posteriorly than anteriorly. Small areas were found on the left arm, on the left forearm, at the base of the right thumb, over the left patella, and on the inner aspects of both thighs—these varying in size from one-half to three inches in diameter. A very large area extended from the level of the first lumbar vertebra to the coccyx, and from the region of the right trochanter around the left thigh posteriorly as far as the left anterior superior spine. This last was the largest of all the areas, and was very edematous. A large area covered the posterior aspect of the right leg, leaving the anterior surface free. A similar area, smaller, however, was present on the posterior aspect of the left leg, just above the heel.

**Feet:** The right foot, including the toes, showed marked discoloration, extending as far as  $2\frac{1}{2}$  inches behind the great toe on the plantar surface, and as far as  $3\frac{1}{2}$  inches above the ankle on the dorsal surface. The toes and the ball of the foot were black. Large bullæ were present on the inner aspect, as well as on the dorsum of the right foot. The largest was  $2\frac{1}{2}$  by 3 inches in diameter, and filled with a dark-reddish serum. The left foot corresponded to the right, except that the two external toes were not involved, the line of demarcation extending diagonally from the base of the third toe to a point two inches behind the base of the great toe, and on this area there was a bulla,  $2\frac{1}{2}$  by  $1\frac{1}{8}$  inches in diameter. A fine line of bright green color was distinctly, although faintly, to be seen tracing the outline of the areas on both feet, but was not to be seen about the lesions elsewhere on the body. (This may have been due to the fact that the lesions on the feet were the first, in point of time, to appear, and were therefore further developed.) The toes, except for the last two of the left foot, were gangrenous; these parts, however, as well as the lesions elsewhere, did not show the sharp line of demarcation seen in dry gangrene.

Pin-point-sized, reddish areas were found over the right thigh at its lower part, and also to a lesser extent over the left thigh. These were not elevated above the surrounding skin, and their color could not be expressed on pressure. A number of similar, pin-point sized areas were seen scattered over the abdomen and thorax.

The skin over the chest and abdomen showed desquamation, which would correspond to a fine scarlatinal desquamation.

**Glands:** The posterior chain of cervical glands, bilaterally, were markedly enlarged. The axillary glands were also enlarged, some being as large as a small bean. The glands in the groins were slightly enlarged.

**Visceral Cavities:** The omentum contained a small amount of fat, and extended down to the pubis. The transverse colon was U-shaped, and extended down to the umbilicus. The peritoneum was everywhere smooth and glistening. The appendix was long ( $4\frac{1}{4}$  inches), and lay over the brim of the pelvis. The spleen did not come down to the costal arch. The diaphragm on both sides extended upward to the third interspace. The breast-plate showed no change. The thymus gland measured  $2\frac{1}{2}$  by  $\frac{1}{2}$  inches, extending downward as far as the second rib. The pleural cavities were free from fluid and adhesions. The pericardium contained the usual amount of clear fluid.

**Lungs:** The left lung floated high in water, contained no solid areas, and showed but slight anthracosis. Section of the lung was pale and dry, otherwise normal. The surface of the left lung showed two pin-point-sized hemorrhagic spots, bright red in color. The right lung corresponded to the left, except that there were no hemorrhagic spots.

**Heart:** The right ventricle and right auricle were empty. The right auriculoventricular orifice admitted the thumb. The left ventricle and left auricle were empty. The left auriculoventricular orifice admitted the finger-tip.



The pulmonary, tricuspid, and aortic valves were normal. The posterior leaflet of the mitral valve showed pin-point-sized elevations, apparently covered by endothelium, these being just above the line of attachment of the chordæ tendinæ.

Neck: The esophagus was normal. The tongue was somewhat flabby. The tonsils were enlarged, but showed no gross pathologic change. The cervical lymph glands were large, as before mentioned, but showed no distinct pathologic change. The thyroid showed no changes.

Spleen: Soft; the capsule wrinkled; the size is  $4\frac{1}{2}$  by  $2\frac{3}{4}$  by  $\frac{7}{8}$  inches, and the estimated weight was between 130 and 150 gm. The splenic pulp was unusually prominent and fairly firm in structure.

Kidneys: Pale, of approximately normal size, with fetal lobulations present. The capsule stripped with slight difficulty, tearing the kidney substance but little. The relation of cortex to medulla was 1 to 2 or  $2\frac{1}{2}$ . The glomeruli were quite prominent and of a reddish color. The medulla was slightly darker than the cortex.

Liver and Gall Bladder: Liver appeared pale on section, and the markings were less distinct than normal. It had a "boiled" appearance. Size, 8 by 6 by  $4\frac{1}{2}$  inches. The gall bladder was moderately distended. There were no calculi.

The pancreas was pale, but otherwise showed no changes. The intestines were normal, excepting for a moderate hyperemia in spots. The stomach showed no changes. The mesenteric glands were enlarged, some as large as small beans, showing hyperemia.

Genital and Urinary Organs: Both right and left broad ligaments showed extensive subperitoneal hemorrhages. The right ovary showed a similar hemorrhagic area,  $\frac{1}{2}$  by  $\frac{1}{4}$  inch. The uterus was infantile. The urinary bladder extended two fingers above the symphysis pubis, and showed a hemorrhagic area on its mucous surface, irregularly  $3\frac{1}{4}$  inches in diameter, purplish-black in color, and slightly elevated above the surrounding mucous membrane. This area was mainly on the right side, extending almost to, but not involving the urinary orifice. The vagina was normal. The uterus was very small, and showed no changes. The right ovary on section showed a hemorrhagic area, occupying more than half of the organ. Near the hilum of this ovary was a cystic body containing clear fluid, 3 mm. in diameter. The left ovary was normal on section. The entire pelvic cellular tissue was infiltrated with bloody fluid.

The aorta showed no changes.

*Anatomical Diagnosis.*—Anemia. Disseminated hemorrhagic subcutaneous infiltration, accompanied in part by gangrene (feet). Hemorrhagic infiltration of the pelvic fascia, of the submucosa of the urinary bladder, and of the right ovary. Hyperplastic cervical lymphadenitis. Hypertrophied tonsils. Persistent thymus (moderate size). Cloudy swelling of the liver and kidneys. Fetal lobulation of the kidney. Hyperplasia of the mesenteric lymph glands. Acute splenitis (mild).

*Histological Examination.*—The skin in the region of the purpuric areas showed extensive changes. The stratum corneum was in part separated into layers and gave one the impression as if it had been dried. The stratum germinativum showed vesiculated areas ranging in size up to a hundred microns in diameter, and the fluid contained therein appeared to be partly within the cells and partly free within the tissues. Polymorphonuclear cells were numerous in this layer. In no place did these vesicular areas reach the stratum granulosum. The cutis vera showed marked necrosis and many vesicular areas similar to those seen in the stratum germinativum, these being located chiefly immediately beneath the stratum germinativum, but a few were slightly deeper. The cells of the ducts of the sweat glands showed some degeneration. In the lower layer of the cutis vera, and in the subcutaneous tissue adjacent to it, was seen quite a marked infiltration of cells, chiefly polymorphonuclear leucocytes. In the same tissues

were areas containing numerous free red blood corpuseles, these latter showing marked evidence of degeneration. The subcutaneous tissue exhibited free blood, was necrotic, and showed in places marked infiltration of polymorphonuclear leucocytes. The lymph glands showed marked hyperemia. The interstitial tissue of the lungs showed marked infiltration, and some of the alveoli contained serum with polymorphonuclear and mononuclear cells. The infiltration in the alveoli and the interalveolar walls was not uniformly distributed, but occurred in more or less separated patches, evidently an early bronchopneumonia. The blood vessels of the lungs showed an unusual number of white blood cells as compared with the red cells. The liver showed moderate cloudy swelling. The spleen showed no marked change. The kidneys showed an acute nephritis; the capsule of Bowman was moderately distended; the epithelium of the convoluted tubules was degenerated, some of the cells being necrotic, and there was a slight infiltration of round cells.

*Bacteriologic Examination.*—Cultures on bouillon and agar slants, from the heart's blood, and from the serum contained in the large bullæ, showed no growth after twelve, twenty-four and forty-eight hours. Smears taken from the splenic pulp show no micro-organisms.

#### SUMMARY

In interpreting the pathologic findings in their relation to the clinical manifestations one must conclude that there is nothing in the gross or microscopic pathology of this case to explain the disease process adequately. The hematuria and frequent urinations were due, in part at least, to the submucous hemorrhage in the bladder, and further than that there is nothing of a gross pathologic nature which stands in the relation of cause and effect to the clinical manifestations.

It is unnecessary to dwell on the impressive—one might almost say dramatic—clinical picture which the patient presented. There was nothing unusual in the course of the attack of scarlet fever preceding the purpura. All the cases in this epidemic were "mild," and this case was no exception. The patient's convalescence was prompt and seemingly uneventful up to the onset of angina on the seventeenth day, but from that time on the stormy course of events clearly showed that some grave general disturbance was going on. First, the angina and cervical adenitis was intense, but rapidly subsided, so that by the third day it had almost entirely disappeared; then succeeded the onset and rapid development of the purpuric areas, each preceded by a peculiar sensation of burning at the point where, in a short hour or so, the purpuric spot was sure to appear. The symmetrical distribution of these areas was evident and in such location as to preclude entirely the idea of the affection being due to thrombosis or embolism. Then came the beginning and progress of gangrene of the toes and the adjacent part of the foot, where the skin lesion had reached the most advanced stage of development, and ultimately the formation of bullæ over the gangrenous areas. The sudden development of intense anemia, during the night preceding

death, reminded one of a chemical reaction, so complete was the change in the general picture that the patient presented. Before, the purpuric areas were on an apparently normal skin, but from that night on there was a great contrast between the dark purpuric areas and the waxen white skin of grave anemia. Last, but none the least dramatic, was the uncanny acuteness of mental activity which was retained to the very last moments before death.

These special features do not appear to be peculiar to this case, but are repeated time and again in the reports of such cases as have reached the literature.

#### CASES ABSTRACTED FROM THE LITERATURE

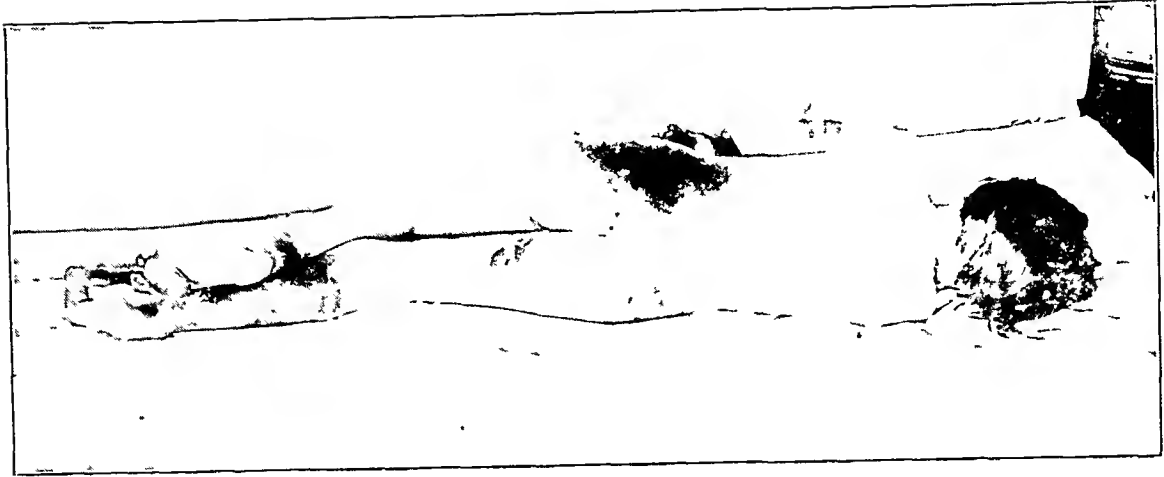
Henoch first described this affection in 1886, and gave it the name "purpura fulminans," at which time he was able to report 4 cases. In 1892 Clara Dercum was able to report on 21 cases, and Joseph Stybr, in 1906, reported 13 cases. As far as is known to me, these three authors are the only ones who have attempted to assemble these cases for a collective study.

Since the publication of Henoch's paper, reports of isolated cases have occasionally appeared in the medical journals, until at the present time it is possible to report on 56 cases, all told. Of these, 32 are reported under the title "purpura fulminans," 10 as rapidly fatal cases of purpura hemorrhagica, 8 as various forms of skin gangrene, and 1 as a "rare sequela of scarlet fever."

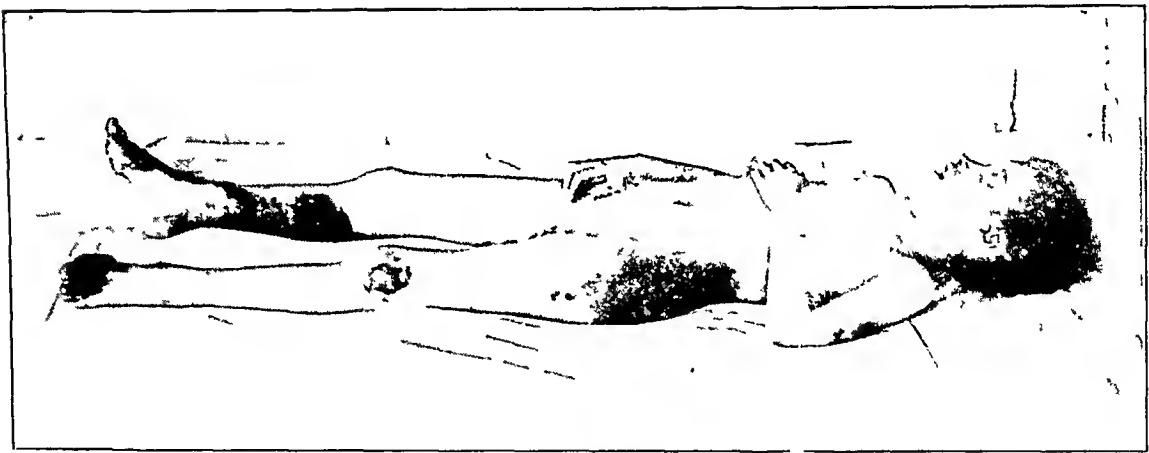
The following 9 cases appear to be similar to my case. In all the purpura appears as a sequela of scarlet fever, during the second or third week of convalescence.

CASE 2 (HENOCH, CASE 2).—Patient, a girl, 2½ years old, said to be recovering from scarlet fever of two weeks previous, with desquamation still present. Three days before admission, purpuric spots appeared on both legs. Examination showed marked anemia, left arm swollen and blue-red, partly black, to the shoulder. Both legs were covered with ecchymoses. Many bullæ were present. Urine was normal. Temperature was 37.5 C. Death took place three and a half days from the onset of the purpura. Autopsy entirely negative.

CASE 3 (DAVIES).—*History*.—A boy, aged 9, while in the third week following scarlet fever, awoke one morning complaining of pain and tenderness in his legs, immediately after which ecchymoses appeared on the posterior surfaces of the legs, on both shins, and on the dorsum of the left foot. At 1 p. m. the calves of both his legs were covered by bluish-black purpuric areas. There were many ecchymoses scattered over the legs, especially about the ankles, confluent in spots, and somewhat edematous. At 9:30 the next morning many of the patches had become confluent, of a raven-blue color, and showed a symmetrical distribution. Tenderness of the legs was extreme. The temperature was normal; pulse, 120. By 1 p. m. all the patches had increased in size, and new ones had appeared on the elbows and hips. The left elbow joint was considerably swollen. Fever developed; pulse was 140. The mental state was clear until death occurred at noon of the second day, thirty hours after the appearance of the first purpuric spot.



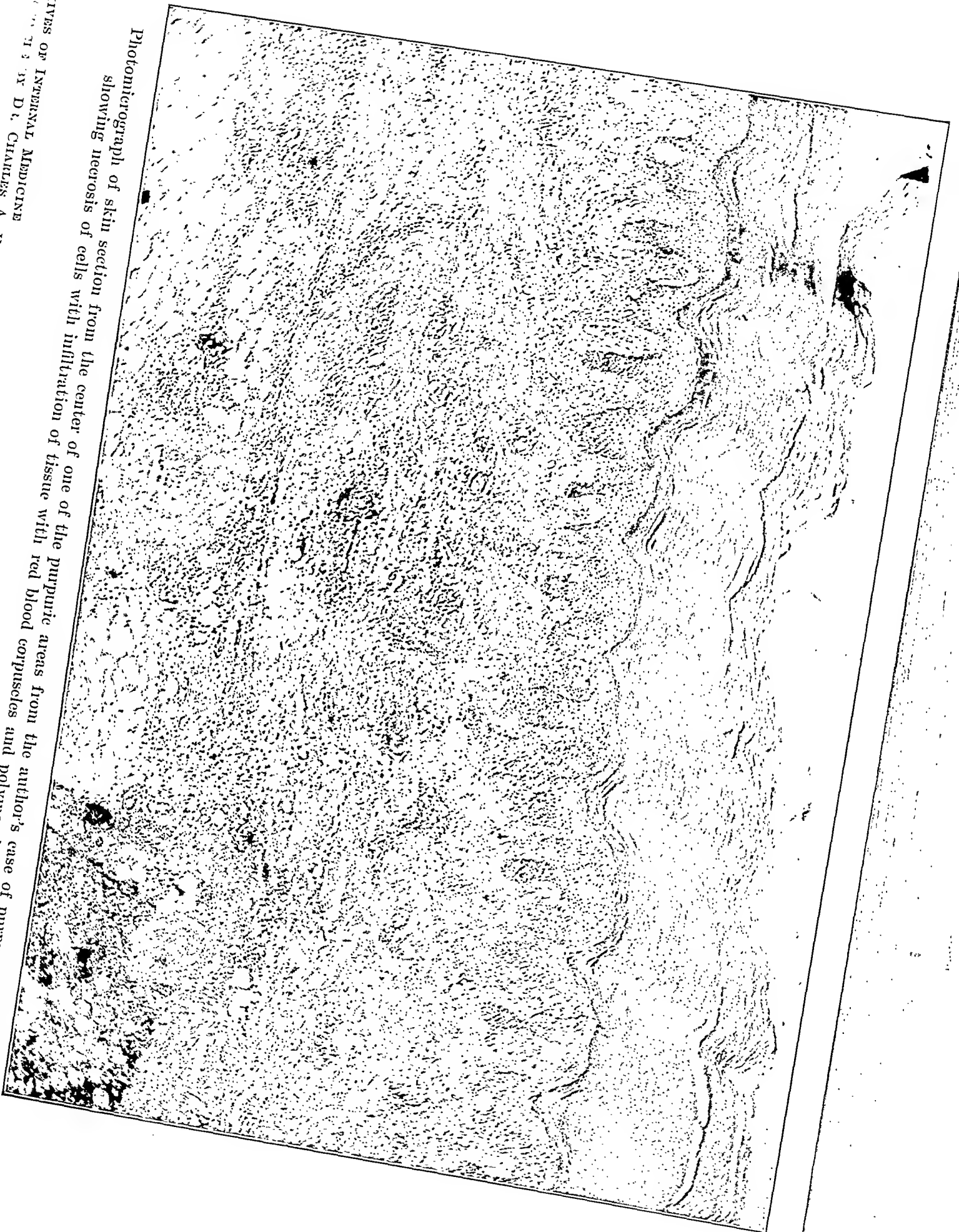
Postmortem photograph of author's case of purpura fulminans; posterior aspect.



Postmortem photograph of author's case of purpura fulminans, showing the symmetrical distribution of the purpuric areas and the gangrene of the toes.



Photomicrograph of skin section from the center of one of the purpuric areas from the author's case of purpura fulminans, showing necrosis of cells with infiltration of tissue with red blood corpuscles and polymorphonuclear leucocytes.





*Autopsy.*—This showed extensive, symmetrical, blue-black areas on the legs, thighs, back and elbows. General anemia was extreme. The blood was fluid, without clots. Pleural cavities contained blood-stained fluid. The autopsy was otherwise negative.

CASE 4 (RISEL).—*History.*—A boy, aged 3 years and 10 months, who had had scarlet fever in a mild form, on the sixteenth day following had nose-bleed, and the mother noticed a purpuric spot on the leg, which spread rapidly. Next day the attending physician reported that there were purpuric areas on both elbows, both calves, and over both malleoli. On the third day the areas had extended markedly, becoming confluent and covering almost all of the posterior surface of the body. A large bulla, filled with bloody serum, was present over the base of the right great toe. The child had pain in the affected areas, anemia became intense, and death occurred at the end of seventy-two hours from the appearance of the first purpuric area.

*Blood Examination.*—Red blood corpuscles, 5,180,000; white blood corpuscles, 38,120; no nucleated reds. Differential count gave: Neutrophils, 83.3 per cent.; lymphocytes, 10.4 per cent.; transitionals, 2.1 per cent.; eosins, 0; basophiles, 2.1 per cent.; myelocytes, 2.1 per cent. Blood platelets were present, but not markedly increased in numbers. Cultures from the blood obtained from heart puncture, three-quarters of an hour postmortem, were sterile after twenty-four hours, but showed staphylococci (probably skin contamination) after forty-eight hours.

*Autopsy.*—Intense anemia of all of the internal organs, but no hemorrhages; blood vessels normal; spleen and bone marrow normal; findings otherwise entirely negative.

CASE 5 (COLLIE).—*History.*—A boy, aged 9, during the third week following scarlet fever, was admitted to the hospital with extensive ecchymoses over the extensor surface of the left elbow and forearm, over the left hip and over the posterior surface of each leg. He complained of extreme tenderness of the skin, and the sensation of "pins and needles" in the affected areas. There were no mucous membrane hemorrhages. The urine was clear and his intelligence acute to Pallor was extreme. The patient's mind was clear and his intelligence acute to his death, forty-eight hours from the onset of the purpura.

*Autopsy.*—A large ecchymosis covered the back, extending from the shoulders downward; otherwise the purpuric areas were symmetrically disposed. The blood was fluid, without clots. The organs were anemic. There was no extravasation of blood into any of the internal organs.

CASE 6 (STRÖM).—The patient, a boy, 2½ years old, who had had a mild attack of scarlet fever, some time later complained of pain in the right leg, which began to swell and became blue-black to the knee. He had fever and headache, and there was a discharge of bloody mucus from the nose. Ecchymoses appeared on the arms, the hands, both legs and in the lumbar region. The right leg was completely discolored to the knee, with a sharp line of demarcation. The urine contained albumin. Death occurred in forty-eight hours after the first appearance of purpura. There was no autopsy.

CASE 7 (DERCUM).—A boy, 4 years old, robust and under good hygienic surroundings, on February 3 felt sick, vomited, and had a scarlet rash on the trunk. The throat was sore, and the cervical glands were swollen. The patient was not confined to bed, and there was no subsequent desquamation. On February 11 the mother noticed, in the early morning, that the boy was pale and feeble, and that there was a purpuric area, the size of his hand, on the outer side of his right thigh, which by 10 a. m. was much larger, and at that time a similar area was noticed on the outer side of the opposite leg. Both areas increased rapidly in size. There was a slight nose bleed in the afternoon. Examination in the evening, forty-five minutes antemortem, showed the child restless and distressed,



with extreme pallor, hurried respirations, rapid pulse, and mind clear. The whole left leg, from the knee to the toes, was of a uniform blue-black color; the right thigh, in its entire circumference, from the groin to the knee, the same. There was a small patch, the size of a quarter, on the outer side of the right leg. The skin was cold and slightly swollen over the purpuric areas. Death occurred fifteen hours after the appearance of the first purpuric spot. There was no autopsy.

CASE 8 (LUND).—A child, aged 6 or 7, had had a mild attack of scarlet fever, and was convalescent, when fever developed and ecchymoses appeared, first on the lower extremities, then on the shoulders and trunk, and rapidly increased in size and numbers. Death occurred in forty-eight hours after the appearance of the first ecchymosis. There was no autopsy.

CASE 9 (WILSON).—Symmetrical gangrene following scarlet fever. The patient, a boy, aged 6, had had a severe scarlet fever, was convalescent ten days, and on the nineteenth day following the onset of the fever had a severe cervical adenitis. On the twenty-fourth day he had pain in the sacral region, and on examination a purpuric spot, two inches in diameter, was noticed over the sacrum. The patient had epistaxis, at first slight, then continuous until death. Soon after the epistaxis commenced, a discoloration of the surface of the nose was noticed, and in one hour the greater part of the nose was blue-black in color, and the discoloration spread rapidly to the cheeks and eyelids. The area over the sacrum, irregularly 3 by 5 cm. in diameter, was gangrenous, and had small blebs on its surface. The patient's mind was clear until one hour before death, which took place twenty-five days following the onset of the scarlet fever, six days following the cervical adenitis, and twenty-five hours following the first appearance of purpura. There was no autopsy.

CASE 10 (HUEBNER).—Skin gangrene following scarlet fever. The patient, a boy, on Dec. 21, 1907, was taken with scarlet fever, and on Jan. 1, 1908, while convalescent, was taken sick with angina and cervical adenitis. On January 1<sup>st</sup> he had pains in various joints, followed by the appearance of blue-black areas in the skin over the elbows, the dorsum of the right hand, the buttocks, and the inner side of the ankles. The progress was very rapid, the areas extending, and the affected skin over the right elbow became gangrenous, with the appearance of bullæ.

This patient gradually recovered, the gangrenous skin over the right elbow became separated, and the surface granulated over, but at the time of reporting, five months later, was not entirely closed. The area over the right elbow was the only one of the purpuric areas that became gangrenous.

This case is not reported as one of purpura fulminans, but it corresponds so closely to the manifestations of this affection that I feel justified in classifying it as such.

The following 5 rapidly fatal cases appear clinically as cases of pure purpura, there being no mucous membrane hemorrhages, gangrene or evidence of internal hemorrhage:

CASE 11 (VANDEVENTER).—A healthy, well-developed boy, 14 months old, without other manifestations, suddenly developed purpuric areas in the groins, which rapidly spread, symmetrically covering the thighs, as far as the knee joints. There were no other manifestations, no fever, no gastrointestinal symptoms, and no mucous membrane hemorrhages. The child died sixteen and a half hours after the first appearance of purpura. There was no autopsy.

CASE 12 (RACHFORD).—An idiotic, epileptic boy, 9 years old, under poor hygienic conditions, suddenly developed purpuric patches on the scrotum, abdo-

men and thighs. The areas increased rapidly in size, became confluent, producing a uniform discoloration about the hips and thighs. There were smaller spots scattered elsewhere over the body. There was no bleeding from the mucous membranes and no other manifestations. Death occurred within twenty-four hours after the first symptoms. There was no autopsy.

CASE 13 (STYBR).—A healthy child, 2 months old, suddenly developed purpuric spots over the body, which rapidly spread, so that in twenty-four hours both thighs, the scrotum and the trunk were covered. The child became very anemic. There were no mucous membrane hemorrhages. Death ensued. There was no autopsy.

CASE 14 (ROTCH).—An infant, 7 months old, always perfectly healthy, and without previous symptoms, suddenly developed a severe form of purpura. Large ecchymoses appeared on the buttocks and on the trunk. The infant rapidly failed in strength and died in twenty-four hours. There were no mucous membrane hemorrhages. No autopsy was made.

CASE 15 (GAILLARD AND HUERTAS).—A case reported as purpura fulminans. An infant of 13 months was apparently well and playing around, when the father noticed that the child's hands were purple. Soon afterward similar patches appeared on the feet; in half an hour the legs were involved, and shortly afterward the thighs and lumbar region. The color of some of the areas seemed to disappear, but reappeared, although the infiltration persisted. The child became comatose and died twenty-eight hours following the first appearance of purpura. There was no autopsy.

The following 4 cases were associated with intense mucous membrane hemorrhages. Henoch considered that purpura fulminans was not associated with mucous membrane hemorrhages, but since his paper appeared (1886) a number of undoubted cases, complicated by hemorrhages from various mucous membranes, have been reported.

CASE 16 (PUCCI).—A boy, 7 years old, had an attack of measles, complicated with parotitis. The parotid was incised and pus evacuated. Two days later bleeding occurred from the nose, mouth, rectum and bladder. Fever developed. In a few days purpuric spots appeared over the entire skin, in many places confluent. There were pains in the limbs; anemia became intense, and a splenic tumor developed. Death occurred two days following the onset of the purpura. No autopsy.

CASE 17 (BOURREIFF).—*History*.—A soldier, 22 years old, was taken suddenly ill. Great pallor of the face was noted and a number of petechiæ were found on the face and temples. There had been hematuria, which was profuse and was repeated. There was bleeding from the mouth and gums, with abundant hemoptysis. New purpuric areas appeared in rapid succession on the forearms, buttocks and abdomen, spreading rapidly. Consciousness was maintained until death, about eight hours following the onset.

*Autopsy*.—This showed extensive ecchymoses in the skin, many hemorrhages into the mucous membranes generally, and into all of the solid organs. The blood was fluid; otherwise no findings, and especially nothing to suggest a cause for the affection.

CASE 18 (APPENRODT).—*History*.—An anemic child, 9 months old, suddenly had nosebleed, vomited bloody mucus, and the entire body became covered with purpuric spots in a remarkably short time. The next day there was an intense general pallor and the purpuric spots had increased in size and number, large confluent areas being present on the arms and legs. The patient passed bright red urine without clots. The entire posterior surface of the right arm became

blue-green in color. There were hemorrhages into the surface of the tongue. Physical examination was negative. The child passed numerous black stools, and death occurred at the beginning of the fourth day.

*Autopsy.*—The abdomen only was examined. Peyer's patches and the mesenteric glands were swollen; there were hemorrhages into the kidney substance, and a subperitoneal hemorrhage in the region of the right kidney; the liver was pale; the spleen was not enlarged; the findings otherwise negative.

CASE 19 (JACKSON).—A boy, aged 5, had had measles the month previous, became feverish and restless. On examination a few purpuric areas, about half an inch in diameter, were noticed on the legs and back, and a small hemorrhagic bulla was noted on the lower lip. The next day profuse hemorrhages occurred from the nose, and the child vomited blood and passed blood in the stools and urine. The hemorrhages from the mucous membranes continued, and the purpuric areas in the skin extended rapidly, becoming confluent. Death occurred on the third day. No autopsy.

The 4 following cases, together with my case and Cases 9 and 10, illustrate the fact that the purpuric areas may become gangrenous if the patient is not overcome before gangrene has time to develop. It may be symmetrically distributed, but is not always so, nor is it always fatal.

CASE 20 (SOUTHEY).—*History.*—A girl, 2 years and 9 months old, who had had an attack of febrile purpura two months previous, complained of pains in the legs. On examination two slate-colored patches were noticed on each calf, which, when massaged, caused the child to cry out with pain. The areas spread rapidly, and new ones appeared symmetrically on the extensor surface of both arms and on both buttocks. On the next day she was admitted to the hospital, at which time both legs from the pelvis down, both upper arms, both buttocks, and, both tronechanters, were of a uniform blue-black color. The face and unaffected skin presented an ashen pallor. The mind was clear. Temperature was 99.4; pulse, 120. The urine contained albumin, but no casts or blood. The patient had repeated convulsions and died thirty-two hours after the first appearance of purpura.

*Autopsy.*—The arteries and veins of the lower extremities were dissected out, and were found to be entirely free from clots or emboli. The blood everywhere was fluid, resembling black cherry juice, and no clots were found. The spleen was slightly enlarged. The brain was free from gross pathologic changes. Otherwise the findings were entirely negative.

CASE 21 (CHARON).—A boy, 3 years old, had always been healthy. The mother noticed a purpuric spot, the size of a two-franc piece, on the dorsal surface of the left foot, which soon increased to tenfold the original size, turned black, and spread to the inner four toes. Similar areas appeared elsewhere on the trunk and extremities. The patches were gangrenous, and blebs developed on them, containing red serum. Pallor of the face was intense. An eclamptic attack occurred and death resulted at the end of the third day. Autopsy showed only anemia of all organs.

CASE 22 (GIMARD, CASE 1).—A boy, aged 8, on admission had an enormous blood tumor on the right side of the face, which occupied the cheek, lips and chin. There were symmetrical ecchymoses of deep violet color, covering the surface of both arms to the shoulders. A violet ecchymosis was present on the dorsum of the right foot, and later over the right ear. Gangrene appeared on the cheek and upper lip, and later on the right arm at the shoulder. The upper lip sloughed off, exposing the teeth. The sloughing surfaces discharged abundant pus, gradually separated and granulated over. Skin grafting was only partly

successful. The wounds cicatrized and the patient was in good health at the time of reporting.

CASE 23 (GIMARD, CASE 2).—*History*.—A boy, aged 14 years, complained of pains in the legs and right buttock. On examination the legs seemed to be paralyzed, and purple ecchymoses were present on the right buttock and on the arms, especially over the elbows. The area over the right elbow became gangrenous. Intestinal hemorrhage occurred, which was repeated, and death came on the twenty-fourth day after admittance.

*Autopsy*.—This showed recent pleural adhesions, fatty degeneration of the liver, three small infarcts in the spleen, a few hemorrhagic spots in the mucosa of the duodenum, but the findings were otherwise negative.

The 10 following cases illustrate the extreme rapidity with which this affection may lead to a fatal termination. Death occurred in two cases at the end of five hours after the first appearance of purpura, and in all within twenty-four hours.

CASE 24 (AUSSET).—A rickety infant of 18 months had had gastrointestinal disturbance, with irregular periods of fever, for weeks. At 5 a. m. a purpuric spot was noticed on the right forearm, which spread rapidly, so that by 9 a. m. the anterior part of the arm had a uniform purple color. Large ecchymoses appeared on the inner aspects of the thighs, over the scrotum, and over the right abdomen and chest. Physical examination was negative. The pupils were unequal. The child became comatose and died at 10 a. m. Autopsy showed a small tuberculous focus in the right lung, fatty degeneration of the liver, and a remarkable lengthening of the intestinal tube.

CASE 25 (ZUELCHAUER, CASE 2).—An evidently healthy, although delicate, girl, 2½ years old, was suddenly taken sick with diarrhea during the night. At 7 a. m. the child was found to be very pale, and a purpuric area was found covering the chin, with many smaller areas on the cheeks, forehead, neck, breast, back and lower extremities. The child's strength failed rapidly, the skin became cool, the pulse soon became imperceptible, and death occurred, without further manifestations, at the end of five hours. No autopsy was held.

CASE 26 (NICOD).—A child, 4 years old, of good antecedents and in good health, was suddenly taken with vomiting which persisted during the night. In the morning this patient complained of pain in the leg, and on examination a purpuric spot, the size of a five-franc piece, was found at the site of the pain. One hour later several more ecchymoses appeared, which rapidly spread, became confluent, and covered the entire body, the skin surface being one purpuric ecchymosis. Death occurred within eight hours from the appearance of the first purpuric spot. There was no autopsy.

CASE 27 (HERVÉ).—An infant girl, aged 3 months, was taken suddenly ill. Examination showed a dozen hemorrhagic patches, the size of a ten-cent piece, scattered over the legs, thighs and abdomen. Three hours later the areas were much more extensive, including the face, forehead and eyelids. The child cried incessantly, but took the breast with avidity. There were no mucous membrane hemorrhages. Death occurred nine hours from the onset of purpura. No autopsy was made.

CASE 28 (LERBER).—A rickety girl, 13 months old, had had bronchial catarrh the month previous. During the night the child suddenly became restless, fever developed, and she appeared very anemic. At 7 a. m. the anemia was intense, and numerous purpuric spots, the largest the size of a five-cent piece, were present on the chest, back and legs. The pulse was rapid. At 9 a. m. the pur-

purpuric areas had become very large, and by 11 a. m. the surface of the back, buttocks, thighs and legs was one continuous blue-black area. The lower lip became blue-red. Death occurred at 1 p. m., twelve hours from the onset. No autopsy was made.

CASE 29 (PICKARD).—A boy, 15 months old, had a chill, followed by a fever of 102; pulse was 130. The child apparently had pains in the abdomen; became pale and restless, and vomited. A few hours later purpuric areas appeared, rapidly covering the legs, but less extensive on the abdomen and face. The right ear became purple. Death occurred within thirteen hours. There was no autopsy.

CASE 30 (GUELLIOT, CASE 2).—A healthy girl, 3 years old, was suddenly taken with a chill, followed by convulsions and vomiting. Purpuric areas appeared scattered over the skin surface, which increased rapidly in size and number, especially over the thighs and trunk. Death occurred at the end of fourteen hours from the first attack of vomiting. There was no autopsy.

CASE 31 (WOLFF).—*History*.—A poorly nourished boy of 2 years and 9 months, was put to bed at 10 p. m. in evident good health, but awoke at 1 a. m., vomited, and had diarrhea. At noon he became dyspneic and complained of pain in the arms and legs, and purpura was noticed in small areas scattered over the body surface, there being one area, 7 by 3 cm. in diameter, over the sacral region. The purpuric areas developed rapidly, so that by 4 p. m. the whole body was covered and death occurred without further manifestations, fifteen hours after the onset of the illness.

*Autopsy*.—This showed swelling of Peyer's patches, mesenteric glands, and spleen; injection of the meninges; petechial hemorrhages into the mucosa of the gastrointestinal tract and bladder; enlargement of the left adrenal. The findings were otherwise negative.

CASE 32 (GUELLIOT, CASE 3).—A strong and vigorous boy, 10 months old, suddenly became dyspneic and very ill; respirations were 96 per minute; pulse slow; extremities cold. Physical examination was negative. Purpuric areas were present upon the thighs and over Scarpa's triangle. The areas increased rapidly in number and size, almost covering the body, becoming confluent in the lumbar region and making the entire body appear almost uniformly black. Death occurred in twenty-three hours. No autopsy was held.

CASE 33 (ZUELCHAUER, CASE 1).—A 2-year-old child, of poor parents, living in damp and dark apartments, suddenly began to vomit and had diarrhea. The child seemed exhausted; the face was very pale and pinched. Many purpuric spots, of different sizes, appeared on the face, one large one covering the left cheek. The areas became almost black, and death occurred at the end of twenty-four hours. Autopsy showed an infiltration of the subcutaneous tissues, with cherry-red blood; petechial hemorrhages on the surface of the medulla and spinal cord; fluid blood, without clots, in the heart and vessels; findings otherwise negative.

The 3 following cases illustrate the development of bullæ on the purpuric areas:

CASE 34 (ARCTANDER).—A boy, 3 years old, was suddenly taken sick. Blue-red ecchymoses appeared over right foot and lower third of the right leg. The toes of the left foot showed ecchymoses. All the affected areas were swollen and became darker in color. The child was restless and had great thirst. Blisters appeared on the left leg, containing reddish serum. Ecchymoses appeared on the back. Death occurred on the third day. There was no gangrene. No autopsy was held.

CASE 35 (RINONAPOLI).—A child, 2½ years old, forty-eight hours previous to examination had shown a purpuric spot, the size of a quarter of a dollar, below the left buttock. Examination showed extensive petechiæ over the thorax and abdomen, and larger purpuric spots over the flexor surface of the extremities. The skin was very sensitive in the neighborhood of the purpuric spots. In twenty-four hours the areas were more extensive and new lesions had appeared. Bullæ containing bloody serum appeared over some of the areas. Death occurred on the third day. There was no autopsy.

CASE 36 (GÖRGES).—The patient, a rachitic boy, aged 2 years, had had an acute gastrointestinal disorder, with fever, which lasted one week. Two weeks later the mother noticed a purpuric spot on the buttock. Next morning the spot was much larger, and, at the same time, a swelling of the right foot was noticed. He was admitted to the hospital on the third day, at which time both ears were found to be swollen and blue-red in color. A bulla was found to be present under the helix of the left ear. Both buttocks, the scrotum and the left wrist were swollen and blue-red in color. The spleen was not enlarged. On the fourth day both hands to the middle of the forearms were dark-red in color, with bullæ present. Many small purpuric spots were found scattered over the general body surface. The wrists and elbows were swollen. Red blood corpuscles, 5,120,000; leucocytes, 18,750. The child made a gradual recovery.

The patients in the 3 following cases had convulsions as a manifestation of this affection, either at the onset or during the course of the disease. That these attacks may have been due to cerebral hemorrhage is not unlikely.

CASE 37 (HENOCH, CASE 4).—A rachitic boy, 9 months old, had an eclamptic attack at 8 a. m. On examination, purpuric areas were found on the nates, upper arms and face. In a few hours the body was covered with dark-red purpuric areas, which spread rapidly and became confluent, especially on the thighs. The temperature rose to 40.8 C. The lungs and heart were negative. There were no mucous membrane hemorrhages. Death took place inside of twenty-four hours. There was no autopsy.

CASE 38 (GUELLIOT, CASE 1).—An infant girl of 7 months, on artificial feeding, had considerable gastrointestinal disturbance. Suddenly the child began to vomit, and had a convulsion followed by coma, with death at the end of fourteen hours from the first vomiting attack. A few moments before the child's death the mother first noticed that the child's body was covered with purpuric spots of a dark purple (some of them almost black) color. There was no autopsy.

CASE 39 (AUDEOUD).—A delicate boy, aged 2½ years, after feeling tired for a day, was noticed to have a purpuric spot on the left wrist. In four hours the body was covered with ecchymoses, varying from the size of a pea to that of a two-franc piece, and the general complexion was of a lead-gray color. The temperature was 40.6 C. By night the ecchymoses on the trunk were much larger, some as large as the palm of the hand, and of a violet color. The surface of the thighs and legs were one continuous diffuse purpuric area. There were no mucous membrane hemorrhages, no edema, and no vesicles. At midnight the child had a convulsion, after which he was comatose until death at 1 a. m., seventeen hours after the onset of purpura. No autopsy was held.

The 2 following cases occurred immediately after exposure to cold and wet, and remind one of hemoglobinuria artificially produced by immersing an extremity in cold water (Hoover and Stone):

CASE 40 (MAILLY).—A boy, 15 years old, frail and of only average health, who worked in a glass factory, where he was exposed to great extremes of heat and cold, and who was forced to live on a scanty diet of salt pork and but few vegetables, went in bathing in a creek, after which he was taken with a chill, and rapidly developed pyrexia, with a temperature of 106. His body became covered with innumerable purpuric spots, averaging in size over 1 mm. in diameter. He complained of pain in the arms, became delirious, went into collapse, the extremities became cold, and he died within twenty-four hours of the initial symptom. There was no autopsy.

CASE 41 (MILLER).—A healthy man, aged 21, after exposure to wet and cold, complained of sore throat and general malaise, and two days later had swelling and pain in the ankles, knees and fingers, at which time purpuric spots were noticed on the feet and legs. Swelling of the joints continued and the purpuric areas increased in number and size, the largest being over the hips, thighs and right shoulder. On the seventeenth day the swelling and pain in the joints had subsided, except for the right shoulder, which by the tenth day was depressed below the surrounding surface, was black, and had the appearance of incipient gangrene. The left eye and tongue became swollen and discolored; the stools were tarry; the urine contained clots, and the sputum was blood-streaked. Ecchymoses were very extensive; and anemia was intense at the time of death on the tenth day. No autopsy was held.

The 2 cases following occurred after pneumonia:

CASE 42 (HENOCH, CASE 1).—A boy, 5 years old, two days following the crisis from a lower-lobe pneumonia, complained of pain in the left leg, and soon afterward a purpuric spot, 9 by 5 cm., was found on his leg. Many spots appeared in rapid succession. Pallor was intense. The entire right leg became blue, and was painful. The urine was clear. There were no mucous membrane hemorrhages. Death occurred in twenty-six hours from the first appearance of purpura. Autopsy showed the pneumonia almost completely resolved; arteries of extremities perfectly free; findings were otherwise negative.

CASE 43 (MAYER).—A 5-year-old boy, of a tuberculous family, had a sharp attack of left upper-lobe pneumonia, ending by crisis on the eighth day, after which he had a good convalescence until the fifth day following the crisis, when a profuse nasal hemorrhage occurred, which was checked by packing the nose. A rhinoscopic examination showed no defect in the nasal mucous membrane. The next day the child was dyspneic, appeared very anemic, and the skin was bathed in perspiration. The nasal hemorrhage recurred and persisted. An artificially produced blister over the liver region contained serum of a blood-red color. On the fifth day following the first epistaxis many small purpuric areas suddenly appeared over the body generally, and rapidly increased in size and number, becoming confluent. The entire left arm became a uniform blue-red color. Death occurred on the eleventh day following the crisis, the sixth day following the first epistaxis, and one day following the appearance of purpura. No autopsy was held.

CASE 44 (BECKMANN).—*History.*—A washerwoman and cook, aged 62, had had vague pains in the extremities, was weak, and had had anorexia for one month. After a restless night she noticed many purpuric spots on the body, passed bloody urine, bloody sputum, and black stools. Examination showed purpuric spots, almost black, over the entire body. Violet-colored ecchymoses were present on the trunk, blue-black areas on the backs of the hands, and the fingertips were black. Bullæ were present on the extensor surfaces of the arms, forearms, and legs. Many small purpuric spots were present in the mucous membranes. Free blood was present in the urine and stools. Death occurred four days after the onset of the purpura.

*Autopsy.*—The blood was fluid, no clots being found. A few petechiæ were found on the surface of the lungs, diaphragm, pericardium and peritoneum. There was hemorrhage into the mediastinum, into the fatty capsule and cortex of the kidneys, and into the mucous membranes of the stomach and urinary bladder. An apoplectic hemorrhage was present in the substance of the right cerebellum. The spleen and liver were slightly enlarged.

CASE 45 (THUE).—*History.*—A 2-year-old, healthy girl complained that she could not walk at 11 a. m.; at 4 p. m. a purpuric spot was first noted on the right ankle and soon after a similar area was found on the opposite ankle. Early the next morning the legs below the knees and the feet, except the toes, were entirely discolored, and new areas, symmetrically located, were found on both trochanters. At 11 a. m. an intense anemia was evident; the child was restless, but the sensorium was clear. Numerous additional purpuric spots appeared, the feet became cold, the child became drowsy, and death occurred forty-seven hours after the first purpuric spot was seen.

*Autopsy.*—This showed an intense anemia of all the internal organs. The purpuric areas showed the cutis vera and the subcutaneous tissue transfused with blood. Otherwise the findings were negative.

CASE 46 (BORGES).—*History.*—A robust boy, 2 years old, had a swelling of the glands of the neck. Eight days later the mother noticed a purpuric spot on the buttocks, and the child was observed to be restless. The next day this spot was much larger and new purpuric areas appeared, symmetrically distributed, on the thighs and legs, and small vesicles were present about the edges of these areas. The areas were large and covered about one-half of the surface of the lower extremities, but were not so extensive on the arms or trunk. There were two small areas on the brow over the left frontal eminence. The skin and mucous membranes were very pale, in marked contrast to the purpuric areas. Death occurred sixty hours after the first appearance of purpura.

*Autopsy.*—This showed fluid blood, without clots; all organs anemic; tonsils swollen; general glandular enlargement, especially in the cervical region; spleen small, otherwise the findings were negative, there being no internal hemorrhage. Cultures gave a pure culture of streptococci from the heart's blood, the spleen, and the cervical glands.

CASE 47 (TYLER).—A woman, aged 25, had an attack of acute articular rheumatism which responded to salicylate treatment. Eleven days later, the patient being seemingly well, a small ecchymosis,  $\frac{3}{4}$  inch in diameter, was noticed at the base of the left thumb, at 7 a. m. At 11 a. m. bleeding occurred from the nose and mouth; she coughed up a few clots, became very restless, and at 3 p. m. the body surface generally was found to be covered with purpuric spots. The ocular conjunctiva and the right eyelid suddenly became suffused with blood. Without other manifestations, death occurred at the end of twenty hours from the time of the appearance of the first purpuric spot. There was no autopsy.

CASES 48-56.—Additional cases are reported by Bacon (two cases), Bouilloche, Brück (two cases), Kerley, Koch, Rilliet and Barthez, and Voss, but these reports present nothing different from those already abstracted, and, to avoid repetition, are not abstracted here.

#### SUMMARY OF REPORTED CASES

Of the patients in these 56 cases, there were 32 males, 15 females, and in 9 (infants) the sex is not mentioned.

As to age, 47 cases occurred under 10 years, 1 at 6 months, and 1 at 62 years.



Predisposing causes are mentioned in 24 cases; scarlet fever 11 times; diarrhea 3; pneumonia, measles and exposure, each 2; vaccination, rheumatism, cervical adenitis and septic infection, each 1. In 32 cases there was no predisposing cause mentioned, and in 17 cases it was definitely stated that the patient was apparently healthy up to the onset of the purpura.

Of 17 cases in which a predisposing cause is mentioned, in 1 the purpura occurred immediately, in 5 within one week, and in all within three weeks of the predisposing factor.

Of the 56 patients, 52 died and 4 recovered.

Of the 52 fatal cases, the average course of the disease was fifty-two and one-half hours from the first appearance of the purpura. The shortest period was five hours, the longest ten days. Nineteen cases were fatal within twenty-four hours, in 10 death occurred on the second day, in 7 on the third day, and in 10 on the fourth day. In 7 the exact time is not given.

As to the size of the purpuric spots, there were extensive ecchymoses covering large areas of skin in 39 cases. In 8 there were innumerable small spots scattered over the body surface, these including 6 of the most rapidly fatal cases. In 9 the exact size of the purpuric spots is not mentioned.

A symmetrical distribution of the lesions was noted 19 times, skin gangrene 8 times, the occurrence of bullæ 9 times, extreme general pallor 13 times.

Pain, occurring at the site of the individual purpuric spots and preceding their appearance, was noted in 12 cases.

Mucous membrane hemorrhages are reported in 18 cases; from the nose, 12; mouth, 4; stomach, 3; intestines, 5; genitourinary tract, 4; conjunctiva, 2; and lungs, 1.

Angina is mentioned in 9 cases, cervical adenitis in 5, and convulsions in 3.

The mental state remained clear to near the fatal termination in a remarkably large proportion of the cases.

Autopsies were held in 20 cases, and aside from a general anemia of the organs in most cases, and visceral hemorrhages in 9 cases, there is a remarkable absence of any gross pathologic change, and nothing that would suggest a possible cause for this affection. Cerebral hemorrhage was found 3 times. In only 1 case was the spleen found markedly enlarged. In 2 cases of symmetrical gangrene the arteries leading to the gangrenous areas were carefully dissected out and were found to be free from any gross pathologic change.

Postmortem cultures were made in 4 cases, twice with negative results; once streptococci were found in all the organs, and once staphylococci were grown from a cardiac puncture taken forty-five minutes after death, but this was considered by the authors reporting the case as contamination from the skin.

From a consideration of the above characteristics of this affection, it would appear that purpura fulminans does not differ essentially from the other forms of purpura. It is a difference in degree only. In purpura fulminans the chemical reaction is complete, the reagent has been added in excess, and the disease progresses with overwhelming finality, whereas in the less severe forms of purpura the chemical reaction is incomplete, the reagent has not been added in excess, and the disease is abortive.

In conclusion, I wish to thank Dr. W. E. Schroeder for the beautiful photographs that he has taken of my patient; Dr. A. A. Goldsmith for conducting the postmortem and making the histologic examination of the tissues; Mr. N. E. Wayson for the bacteriologic examination, and Dr. Carl von Klein for valuable assistance in searching for the reports of cases in the literature.

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#### REFERENCES TO REPORTED CASES

- Appenrodt: *Deutsch. med. Wehnschr.*, 1875-6, i, ii, 463.  
 Arctander: *Hosp. Tid.*, 1887, x, 227.  
 Audeoud: *Rev. méd. de la Suisse Rom.*, 1906, xxvi, 241.  
 Ausset: *Echo méd. du nord.*, 1899, iii, 41.  
 Bacon: *Chicago Med. Recorder*, 1892, iii, 32.  
 Beckmann: *St. Peter b. med. Wehnsch.*, 1891, xvi, 55.  
 Borgen: *Norsk. Mag. f. Laegevidensk.*, 1901, xvi, 463.  
 Boulloche: *Semaine méd.*, 1899, xix, 366.  
 Bourreiff: *Rec. et mém. de méd. mil.*, 1878, xxxiv, 172.  
 Brück: *Orvosi hetil.*, 1888, xxxii, 564.  
 Charon: *Jour. de méd. et chir. et pharm.*, Brussels, 1883, lxxvii, 113.  
 Collie: *Lancet*, London, 1891, i, 658.  
 Davies: *Brit. Med. Jour.*, 1891, i, 458.  
 Dercum: *Med. and Surg. Reporter*, 1892, lxvii, 838.  
 Gaillard and Huertas: *Gas. d. mal. in. et d'obst.*, Paris, 1906, viii, 57.  
 Gimard: *France méd.*, 1887, ii, 1557.  
 Görges: *Berl. klin. Wehnschr.*, 1897, xxxiv, 477.  
 Guelliot: *Union méd. et sc. du nord-est.*, 1884, viii, 25.  
 Henoch: *Prag. med. Wehnschr.*, 1886, xi, 494.  
 Hervé: *Revue mens. d. mal. de l'enf.*, Paris, 1889, iv, 31.  
 Huebner: *Berl. klin. Wehnschr.*, 1908, 1345.  
 Jackson: *Arch. Pediat.*, 1890, vii, 951.  
 Kerley: *Treatment of Diseases of Children*, 1907, p. 183.  
 Koch: *Verhandl. d. Versamml. d. Gesellsch. f. Kinderh.*, 1892, 134.  
 Lerber: *Corbl. f. schweitz. Aerzte*, 1904, xxxiv, 123.  
 Lund: *Norsk. mag. f. Laegenvidensk.*, 1871, 219.

- Mailly: Univ. Med. Mag., 1892-3, v, 202.  
Mayer: Centralbl. f. Kinderh., 1900, v, 380.  
Miller: Medical News, 1891, lix, 156.  
Nieod: Rev. méd. de la Franche-Comté, 1905-6, xiv, 167.  
Piekard: Canada Lancet, 1889-90, 705.  
Pucci: Gazz. d. osp. e d. elin., 1896, xvii, 291.  
Raehford: Medical News, 1892, lxi, 433.  
Rilliet and Barthez: Traité clinique et pratique des maladies des enfants, 1853, ii, 323.  
Rinonapoli: Arch. ital. di pediat., 1889, vii, 92.  
Risel: Ztschr. f. klin. Med., 1905-6, lviii, 162.  
Rotch: Pediatrics, the Hygiene and medical treatment of children, 1906, p. 1024.  
Southey: Tr. Path. Soc., London, 1883, xxxiv, 286.  
Ström: Eira, Gothenburg, 1887, xi, 132.  
Stybr: Casop. lek. cesk., 1906, xlv, 9.  
Thue: Norsk. Mag. f. Laegevidensk., 1901, 463.  
Tyler: Medicine, 1898, iv, 476.  
Vandeventer: Physician and Surg., 1898, xx, 458.  
Voss: Norsk. Mag. f. Laegevidensk., 1901, xvi, 471.  
Wilson: Arch. Pediat., 1895, xii, 679.  
Wolff: Berl. klin. Wehnschr., 1880, xvii, 254.  
Zuelchauer: Berl. klin. Wehnschr., 1869, vi, 176.

# A CRITICAL STUDY OF THE VALUE OF THE MEASUREMENTS OF CHEST EXPANSION AND LUNG CAPACITY

THEIR UNRELIABILITY IN CONDITIONS OF HEALTH AND IN EARLY  
PULMONARY DISEASE

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Two methods of estimating lung capacity have long been employed: 1, the measure of chest expansion as an index of lung capacity, and, 2, spirometer readings as the accurate measure of lung capacity.

Both of these well-known methods are simple in their application, and the measurements themselves can be made with accuracy. These two facts have resulted in their general acceptance as valuable aids in estimating standards of health, but opinions are still divided as to their value in the diagnosis of early pulmonary disease.

The following observations were undertaken in order to determine more exactly the value of both measurements as aids in the physical examination of individuals:

Three questions are to be considered in this study:

1. Can the respiratory capacity be accurately estimated by either or both of these measurements?

2. Are the measure values constant enough in the individual to allow us to accept normal standards?

3. Are the measurements of value in the diagnosis of early pulmonary disease?

A knowledge of the mechanics of pulmonary respiration is essential, first of all, to the proper study of these questions. Briefly, they are as follows:

In ordinary respiration the primary step is the contraction of the muscles of respiration. Roughly, these may be divided into two groups, the muscles attached to the chest and those attached to the diaphragm. The result of their contraction is enlargement of the thoracic cavity, the muscles of the chest increasing the anteroposterior and transverse diameters, the contraction of the diaphragm increasing the vertical diameter. Inspiration results from this thoracic enlargement, owing to the difference in pressure between the air without and the air within the chest. In normal, quiet respiration this inspired air is spoken of as the tidal air.

With forced respiration, the type which more especially concerns us, there is not only a forced contraction of these same muscles, but the accessory muscles of respiration are called into play. Some of these muscles act directly on the chest walls; but of far greater importance is the action of the abdominal walls, the contraction of which forces the diaphragm upward, the important factor in expiration. The additional air which is inspired during forced inspiration is spoken of as the complementary air; that which is expired is spoken of as the supplemental air.

It should be further noted that the greatest increase in the size of the thorax is in the vertical diameter, since less resistance is offered to the movement of the diaphragm as compared with the rather rigid chest walls. Thus respiration is essentially the result of muscular activity. Furthermore, these muscles are under the control of the will. It is evident, therefore, that in the same individual one group of muscles may be brought into play at the expense of the other, which might result in variations in the measure of chest expansion and in the actual size of the thoracic cavity.

In order to avoid the well-known variations due to age and sex, we have selected for our series males between the ages of 20 and 45.

#### I. CHEST EXPANSION

This is the measure more commonly employed, since it is the more convenient.

Individual variations in this measurement are illustrated by the following observations selected from the normal persons.

If we observe the individual who has not been previously instructed, during forced inspiration, we note two general types of breathing. Between these two types all degrees of variation are possible.

1. Quite natural inspiration is intensified. The chest expands and the abdomen protrudes as the diaphragm descends. These two movements follow ordinarily the type of breathing natural to the individual, costal or abdominal. The effort is made with the object of inspiring as much air as possible, and it is probable that under these circumstances the maximum capacity is attained regardless of the particular type natural to the individual. On the other hand, the measure of chest expansion is markedly influenced by the type of breathing, as is shown in Table 1.

2. A decided effort is made by the individual to attain the maximum chest expansion, no special attention being given to the amount of air inspired.

TABLE I.—RELATION BETWEEN CHEST EXPANSION AND TYPE OF BREATHING

Costal Type.		Abdominal Type.	
Expansion.	Capacity.	Expansion.	Capacity.
4.2 inches.	270 cubic inches	1.5 inches	270 cubic inches
3.5 inches	200 cubic inches	1.4 inches	225 cubic inches
3.5 inches	265 cubic inches	1.4 inches	225 cubic inches
3.0 inches	200 cubic inches	1.1 inches	220 cubic inches
3.0 inches	245 cubic inches	1.0 inches	215 cubic inches
3.2 inches	245 cubic inches	1.4 inches	195 cubic inches
2.8 inches	210 cubic inches	0.8 inches	260 cubic inches
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Av. 3.3 inches	233 cubic inches	1.2 inches	230 cubic inches

One observes with this effort a marked retraction, instead of the normal protrusion of the abdominal walls. This results in an additional increase in the chest measurement, because the vertical diameter of the thoracic cavity is shortened as the diaphragm is forced upward. This abdominal retraction may be brought into play either at the end of full inspiration, before inspiration is begun, or before inspiration is completed.

The influence of this voluntary action on the measure of chest expansion, as well as lung capacity, is illustrated in Tables 2 and 3.

The first measurements (Table 2) were taken without previously instructing the individuals.

TABLE II.—EFFECT OF VOLUNTARY ACTION ON CHEST EXPANSION AND LUNG CAPACITY

Expansion.	Capacity.
4.3 inches	180 cubic inches
4.2 inches	180 cubic inches
4.0 inches	140 cubic inches
3.5 inches	135 cubic inches
3.4 inches	180 cubic inches
2.9 inches	165 cubic inches
2.8 inches	140 cubic inches
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Av. 3.6 inches	160 cubic inches

A second measurement was made after instructing the individual to fill his lungs with air and to blow the needle of the spirometer as high as possible, disregarding the expansion of his chest. The results are given in Table 3.

TABLE III.—EFFECT OF VOLUNTARY ACTION ON CHEST EXPANSION AND LUNG CAPACITY

Expansion.	Capacity.
2.8 inches	240 cubic inches
2.6 inches	250 cubic inches
2.5 inches	235 cubic inches
2.3 inches	195 cubic inches
3.0 inches	240 cubic inches
2.1 inches	220 cubic inches
2.2 inches	210 cubic inches
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Av. 2.5 inches	227 cubic inches

Thus in the same individuals considerable variation is possible in both measurements, depending on the mechanics of the respiratory effort, and it is evident that any measurements which disregard the mechanism of breathing may be misleading and erroneous.

Comparing Tables 2 and 3, it is clear that, in the same individual, the increased muscular effort called forth in producing the maximum expansion resulted in an actual loss of lung capacity.

If we take the average of the seven measurements, we find that an increase of 1.1 inches in expansion was attained at a loss of 67 cubic inches of air. With practice this difference is even more marked.

This supports our recent observations,<sup>1</sup> in which it was shown that at least 50 per cent. of the maximum chest expansion may be due to muscular action alone, no additional air being inspired. The explanation of this lies in the fact that if the breath is held the thorax becomes a closed cavity. If now the diaphragm is forced upward by retraction of the abdominal walls, the vertical diameter of the chest is shortened, and the other two diameters are necessarily increased and an increase in the chest measurement results.

From these two tables it is also evident that the measure of chest expansion may be an index of the development of the muscles which expand the chest.

Thus no definite relation exists between expansion and lung capacity; the measure of expansion is an unreliable guide in estimating the capacity of the lungs in normal individuals. It is also to be noted that the maximum lung capacity is best measured by instructing the individual to follow the normal type of breathing and to inhale as much air as possible into the lungs.

#### *May We Accept a Normal Standard of Chest Expansion?*

From the variations shown in the preceding tables, doubt is thrown on the advisability of accepting any measure as a normal standard.

Taken collectively, our cases averaged between 2 and 2½ inches expansion, but individual exceptions are encountered so frequently that the application of this average is inadvisable, because of the fact that extreme types of abdominal breathing invariably give low expansion measurements, and also to the fact that this muscular effort can not always be eliminated, no matter how carefully the individual may be instructed.

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1. Boston Med. and Surg. Jour., 1908, clviii, 761.

The few measurements in the following table taken after carefully instructing the individuals illustrate these two points.

TABLE IV.—EXPANSION AND CAPACITY IN ABDOMINAL BREATHING

Abdominal breathing, Extreme Types of Expansion.		Muscular Contraction Not Entirely Eliminated.	
Capacity.		Expansion.	Capacity.
0.8 inches	260 cubic inches	3.0 inches	195 cubic inches
1.7 inches	220 cubic inches	2.4 inches	195 cubic inches
1.4 inches	240 cubic inches	2.4 inches	185 cubic inches
1.5 inches	275 cubic inches	2.7 inches	185 cubic inches
1.5 inches	235 cubic inches	2.5 inches	195 cubic inches
Av. 1.4 inches	246 cubic inches	2.6 inches	191 cubic inches

The average chest expansion of these 10 selected subjects is 2 inches, but it is evident that this average is without value if it is to be taken as an index of lung capacity, as the individuals with the greatest capacity have the smallest expansion. It is not to be concluded that such a marked difference is the rule. These extreme types are selected to illustrate the fact that individual variations are so pronounced and the mechanism so complicated that the measurements are extremely complicated instead of simple, as is so commonly supposed. This point will be referred to again in the discussion of the measurements of capacity.

## II. LUNG CAPACITY

We have already called attention to the mechanical principles that determine the amount of air inspired during forced inspiration. The individual variations which are possible during inspiration have also been mentioned.

In measuring the lung capacity, however, we still have another factor to consider, namely, the expiration into the spirometer after the forced inspiratory act has been completed. Normally, forced expiration is accomplished chiefly by the contraction of the muscles of the abdominal walls, whereby the diaphragm is forced upward as high as possible.

Of the two groups of muscles, the inspiratory and the expiratory, the latter are the stronger. Thus again we assume that the amount of supplemental air will depend largely on the development of the abdominal muscles, and that with excessive development there is an apparent rather than actual increase in the lung capacity due to the fact that the supplemental air is increased at the expense of the residual air.

Assuming two individuals with the same lung capacity, if the abdominal muscles of one were relatively more developed, he would be able to expire more air than the other; that is, he would have a larger supplemental air, but this would be at the expense of the residual air. Conditions would be reversed in the second individual. Unfortunately, we



have no accurate method of measuring the complementary, tidal and supplemental air.

Approximately 230 cubic inches have been accepted as the normal lung capacity. This represents the average of a large series of measurements of college students and men accustomed to a moderate amount of gymnasium work.

Since so much depends on the muscular development of the individual, as has already been shown, we have, for the purpose of our analysis, divided our subjects into three classes according to their muscular development:

1. Individuals with rather inferior muscular development.
2. Well-developed individuals.
3. Individuals with excessive muscular development.

Examples of the first type were selected from men who sought treatment at an out-patient department for some functional disorder. All had negative physical examinations and none complained of pulmonary symptoms. These individuals lived in the crowded sections of the city; their occupations did not call forth special muscular or pulmonary activity, and in the main the greater portion of the day was spent indoors.

The second series of measurements were taken from students and men who spent a few hours each week in the gymnasium.

For the third series we are indebted to the officers of the U. S. S *Wabash* for the privilege of measuring the blue jackets and marines who were in active service.

The average of these measurements is given in Table 5.

TABLE V.—AVERAGE MEASUREMENTS IN THREE CLASSES OF MUSCULAR DEVELOPMENT

	Chest Measurement.			Lung Capacity.
	Full Expiration.	Full Inspiration.	Chest Expansion.	
1. Hospital patients . . . . .	32.7 inches	34.9 inches	2.2 inches	191 cubic inches
2. Students . . . . .	34.3 inches	36.2 inches	1.9 inches	235 cubic inches
3. Bluejackets and marines.	33.7 inches	36.5 inches	2.8 inches	248 cubic inches

Thus in condition of health the lung capacity varies between 191 and 248 cubic inches. Higher values are possible and even lower values may be present with normal lungs.

Again, our attention is called in this table to the direct relation between muscular development and lung capacity. No such relation, however, is found between the measures of chest expansion and lung capacity. The unreliability of chest measurements is to be explained by the individual variations above mentioned.

This lack of relation between expansion and capacity is well illustrated by a more careful analysis of the series.

Of the 200 hospital patients, 84 had a chest expansion of less than 2 inches, but, of this number, 23, or 27 per cent., had a larger capacity than the average for this type, which was 191 cubic inches.

Of the remaining 116 patients with an expansion of 2 inches or more, 44, or 38 per cent., had less than the average capacity.

Thus wrong conclusions would be drawn in 65 per cent. of the cases if we were to accept 2 inches as the normal chest expansion.

With the students there was a similar error of 44 per cent., and with the blue jackets and marines 33 per cent.

This constant decrease in the error is explained by the fact that with higher degrees of muscular development there is a correspondingly larger number of individuals who attain an expansion of 2 inches. Likewise we assume that the supplemental air is increased at the expense of the residual air in the more muscular men.

This is further illustrated by Table 6, in which the hospital patients are grouped according to their chest expansion measures.

TABLE VI.—HOSPITAL PATIENTS

No. Patients.	Chest Expansion.	Average Chest Capacity.
9	up to 1 inch	151.1 cubic inches
36	1 to 1.5 inches	178.2 cubic inches
39	1.5 to 2 inches	183 cubic inches
48	2 to 2.5 inches	196.5 cubic inches
24	2.5 to 3 inches	196.4 cubic inches
20	3 to 3.5 inches	214.2 cubic inches
14	3.5 to 4 inches	195.3 cubic inches
10	4 + inches	202.5 cubic inches

Thus there is a general yet not constant tendency to an increased capacity as the measure of expansion increased. This increase in capacity, however, is not in proportion to the increase in expansion. The 48 patients with an expansion between 2 and 2.5 inches, an ample expansion for the maximum capacity under all ordinary circumstances, had an average capacity of 195.6 cubic inches. The 68 patients with an expansion of 2.5 or more inches had an average capacity of 202.1 cubic inches, an increase of only 6.5 cubic inches of air.

The students gave a similar increase of 12 cubic inches, the blue jackets and marines of 18 cubic inches.

These relatively small increases in capacity are undoubtedly explained by the same factors that accompany increased muscular development.

#### *Influence of Practice on Expansion and Capacity.*

Without tabulating individual examples, it was evident that both measurements may be influenced by practice in two ways:

## *CHEST EXPANSION AND LUNG CAPACITY*

1. Improvement in the method of breathing, which results in increased capacity with or without increased expansion.
2. Intensification of the muscular effort which results in increased expansion without increased capacity or with only a slightly increased capacity, due to the increased muscular effort in the expulsion of air; in other words, an increased supplemental air.

### *Value of Measurements in Disease of the Respiratory Tract*

When the respiratory tract is diseased, a decrease in expansion and capacity results from two general causes:

1. Loss of strength of the muscles of respiration.
2. Limitations to the amount of air which can be inspired.

The loss of muscular strength usually accompanies the weakness of the entire muscular system. This is illustrated by three cases of chronic lead poisoning with emaciation and general muscular weakness; the patients had an average chest expansion of 1 inch and an average lung capacity of 140 cubic inches. Examination of the lungs in all three cases was negative and there were no pulmonary symptoms.

Limitations to the amount of air which can be inspired result from one of two causes:

1. Actual loss in lung tissue.
  2. Irritability of the air passages, which prevents a full inspiration.
- This irritability shows itself either as discomfort, pain, or tendency to cough.

### *Loss in Lung Tissue*

Diminution of capacity necessarily results from loss of lung tissue. When present it is demonstrable by auscultation and percussion. The measure of capacity can be of value only in estimating the degree.

A series of patients with well-advanced pulmonary tuberculosis gave an average capacity of 97 cubic inches, with an average expansion of 1.25 inches. Values as low as 50 or 60 cubic inches were frequently met with. The largest capacity we obtained was 180 cubic inches. In all these cases simple inspection was sufficient to establish a marked diminution in capacity.

### *Irritability of the Air Passages*

No definite conclusions as to diminished capacity can be drawn until this factor has been eliminated, as is illustrated by the following cases:

Two patients with nasopharyngitis, due to deviation of the septum, had very irritable throats. One had a capacity of 125, the other of 140 cubic inches. Both were muscular men with negative lungs. After the

throats were sprayed with cocaine the patients measured 230 and 250 cubic inches, respectively.

Two mild cases of acute bronchitis, with scattered râles, and but little cough, measured 230 and 245 cubic inches.

Six patients with bronchitis of a similar type, but with laryngeal irritation, averaged 130 cubic inches. After the administration of heroin, the average capacity was 225 cubic inches.

### *Value of These Measurements in Early Pulmonary Disease*

From the observations recorded, it is evident that, in cases of suspected phthisis, considerable doubt is thrown on the values of these measurements as a further aid in diagnosis.

In our hospital cases, the class of individuals in whom phthisis is so often suspected before other physical signs are positive, it was shown that a capacity as low as 190 cubic inches is consistent with a normal lung.

In conditions of debility and anemia, low values may be the result of muscular weakness.

It is not conceivable that, in this early stage of the disease, the actual loss of lung tissue itself would influence the lung capacity to any noticeable degree. The cough which may accompany this stage of the disease may, by means of the irritation, prevent the full muscular effort which results in thoracic enlargement.

We quote this most striking illustration of the negative value of the measurements in early phthisis: A pilot, 43 years old, complained of a slight morning cough. There was very little expectoration. He was somewhat worried about the cough, but otherwise said he had never felt better. There was no loss in weight. There were definite signs at the right apex and many tubercle bacilli in the sputum, yet his chest expansion was 3.5 inches and his lung capacity measured 260 cubic inches.

### CONCLUSIONS

The measure of chest expansion has no constant direct relation to the lung capacity and by itself is of comparatively little value as one of the methods of physical examination. Large measures only indicate good development of the muscles which expand the chest. Owing to individual variations, normal standards can not be adopted. It is probable, however, that an expansion of from 2 to 2.5 inches will permit the maximum capacity under ordinary conditions of health.

In normal individuals the measure of lung capacity varies directly with the muscular development, provided the individual breathes proper-

ly. Erroneous conclusions may be drawn from spirometer readings unless special attention is given to the method of breathing. Capacities of 190 cubic inches, and possibly less, are consistent with normal lungs.

With both measurements large values only indicate good muscular development. Low values indicate inferior muscular development or improper breathing.

In suspected pulmonary disease, very little, if any, additional aid in diagnosis is obtained by these measurements. The only positive value of the measurements is the aid in determining whether or not the person is breathing properly, and whether or not the muscles of respiration are properly developed.

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# THE DISTRIBUTION OF TUBERCULOUS LESIONS IN INFANTS AND YOUNG CHILDREN

A STUDY BASED ON POSTMORTEM EXAMINATIONS \*

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In view of the interest and importance of the question concerning the manner of infection and the localization of tuberculous lesions in the human subject, it seemed that the analysis of the autopsy material at the Babies' Hospital of the City of New York would prove of value in showing the facts in the cases of a number of city-bred infants and young children, the great majority from the most crowded and unhygienic tenement districts, badly fed and badly cared for before entering the hospital in all stages of tuberculosis.

From October, 1889, to July, 1908, 1,131 autopsies were performed, of which 185, or 16.4 per cent., showed tuberculosis of one or more organs. The hospital admits children under 3 years only, and the records show that 60 per cent. of all admissions are of infants under 1 year of age, and that the death rate is exactly three times as high among these young babies as it is among the children from 1 to 3 years old. Of all the autopsies performed, 78 per cent. were on infants under 1 year, and 26 per cent. on infants under 3 months of age, while only 5 per cent. were on children older than 2 years, including four who were 4 years old.

From the 185 cases of tuberculosis we learn that 12 per cent. of all infants under 1 year of age coming to autopsy showed tuberculous lesions, while 36 per cent. of those between 1 and 2 years, and 32 per cent. of those over 2 years, were so affected. Of infants under 3 months of age, but 1.8 per cent. had tuberculosis. These figures are rather higher than those reported by Fröbelius<sup>1</sup> (2.2 per cent.), Orth<sup>2</sup> (3.4

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\*Read at the Pediatric Section of the International Congress on Tuberculosis, Washington, Sept. 28, 1908.

1. Fröbelius (W.): Ueber die Häufigkeit der Tuberkulose und die hauptsächlichsten Localizationen im zartesten Kindesalter. *Jahrb. f. Kinderh.*, 1886, xxiv, 47.

2. Orth (J.): Ueber einige Zeit- und Streitfragen aus dem Gebiete der Tuberkulose. *Berl. klin. Wchnschr.*, 1904, xli, 265.

per cent.), Kossel<sup>3</sup> (6 per cent.) and Sehlbach<sup>4</sup> (7.8 per cent.) in babies under 1 year of age and approach more nearly those of Hamburger<sup>5</sup> (15.4 per cent.) and Trépinski<sup>6</sup> (15 per cent.), whose second-year statistics (34.5 per cent.) also coincide closely with my own. Seventy-eight girls and 107 boys were affected in this series.

The higher percentage of tuberculosis in young infants in these cases may be partly dependent on the fact that many nationalities are comprised among them, living under climatic and other conditions which differ widely from those to which they have been accustomed in their native land, and that overcrowding and lack of cleanliness not only predispose the infants to infection, but make the disease rapidly fatal. That tuberculosis is comparatively less frequent in the first than in the second year of life is borne out by these cases as well as by those hitherto reported.

In analyzing this series of cases it seemed most rational to group them according to the relative age and distribution of the tuberculous lesions, with a view to deducing from such a classification such facts as became pertinent from its study. It is perfectly true that the localization of the oldest lesion is not always synonymous with the point of entrance of the tubercle bacillus, and that the greater number of cases of extensive pulmonary as compared with intestinal tuberculosis by no means proves that all such cases result from aspiration rather than from ingestion of the bacilli. Important in this connection

3. Kossel (H.): Ueber die Tuberkulose im frühen Kindesalter. *Ztschr. f. Hyg. u. Infektionskrankh.*, 1896, xxi, 59.

4. Sehlbach (P.): Ueber die Häufigkeit der Tuberkulose und die beiden Hauptzeitpunkte der Ansteckung mit derselben im Säuglingsalter. *München, med. Wehnsehr.*, 1908, iv, 322.

5. Hamburger (F.): Zur Kenntniss der Tuberkuloseinfection im Kindesalter. *Wien. klin. Wehnsehr.*, 1907, xx, 1069. Comparing Hamburger's figures for the first two years of life with my own, I find:

FIRST YEAR OF LIFE				
	First Quarter.	Second Quarter.	Third Quarter.	Fourth Quarter.
Hamburger . . . . .	4 per cent.	18 per cent.	23 per cent.	
Wollstein . . . . .	1.8 per cent.	11 per cent.	16 per cent.	23 per cent.
SECOND YEAR OF LIFE				
	First Half.		Second Half.	
Hamburger . . . . .			40 per cent.	
Wollstein . . . . .	34 per cent.		44 per cent.	

Thus both Hamburger's figures from Vienna and mine from New York show a progressive number of tuberculous autopsies during the four quarters of the first year and during the second year of life.

6. Trépinsky: Ein Beitrag zur Statistik und Anatomie der Tuberkulose im Kindesalter. Quoted by Fürst (L.): Die intestinale Tuberkulose Infection mit besonderer Berücksichtigung des Kindesalters. Stuttgart, 1905, Ferdinand Enke.

is the fact that has been proved by Orth,<sup>7</sup> Ravenel,<sup>8</sup> Herman<sup>9</sup> and others, that the tubercle bacillus may pass through the normal intestinal wall without any lesion resulting at that point. It may then produce tuberculosis in the mesenteric lymph nodes or it may become localized there for a shorter or longer period of latency, causing the lymphoid stage of tuberculosis described by Bartel and Spieler,<sup>10</sup> which is a pre-tuberculous stage of simple non-characteristic hyperplasia, the tuberculous nature of which can be demonstrated only by means of animal inoculation with the suspected lymph nodes. The studies of Bartel and Newmann<sup>11</sup> show that in the cervical and mesenteric nodes the lymphoid stage tends to be more marked than in the bronchial nodes, which present a greater tendency to cheesy degeneration than do the mesenterics. This latter point is fully borne out by the observation of my cases.

According to the lesions found in my cases, they may be grouped as follows:

- I. Those showing pulmonary lesions only.
- II. Those showing bronchial lymph node lesions only.
- III. Those showing pulmonary and bronchial node lesions.
- IV. Those showing pulmonary and bronchial node lesions as the most advanced lesion of a generalized tuberculosis.
- V. Those showing intestinal and mesenteric lymph node lesions only.
- VI. Those showing intestinal and mesenteric lymph node lesions as the most advanced of a partially generalized tuberculosis.
- VII. Those showing intestinal and mesenteric lesions as the most advanced in a completely generalized tuberculosis.

No case of congenital tuberculosis occurred. Two subjects were 7 weeks old, the youngest in the series. In one the lungs and bronchial lymph nodes were affected, while a few early splenic tubercles gave evidence that hematogenous generalization had begun. The other presented a very generalized tuberculosis, the bronchial lymph nodes showing a more extensive cheesy degeneration than the mesenteric nodes, and the pulmonary lesion being more advanced than any other. The child's

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7. Orth (J.): Zur Frage der Infektionswege der Tuberkulose. Sechste Internat. Tuberkulose-Konferenz, Vienna, Sept. 19-21, 1907, p. 67.

8. Ravenel (M. P.): Sechste Internat. Tuberkulose-Konferenz, Vienna, Sept. 19-21, 1907, p. 102.

9. Herman (M.): Sur la pénétration du bacille tuberculeux à travers la paroi intestinale. Sechste Internat. Tuberkulose-Konferenz, Vienna, Sept. 19-21, 1907, p. 103.

10. Bartel (J.) and Spieler (F.): Der Gang der natürlichen Tuberkuloseinfektion beim jungen Meerschweinchen. Wien. klin. Wchnschr., 1906, xix, 25.

11. Bartel (J.) and Neumann (W.): Ueber experimentelle Inhalationstuberkulose beim Meerschweinchen. Wien. klin. Wchnschr., 1906, xix, 167 and 213.



mother had died of "consumption" during the second week of the infant's life.

### I. PULMONARY LESIONS ONLY

There were four such instances, the tuberculosis in each case being limited to one lung, and consisting of miliary tubercles in two, of an area of cheesy pneumonia in another, and of several small cheesy peribronchial nodules in the fourth. These cases were unquestionably of inspiratory origin. The bronchial lymph nodes were swollen but without macroscopic or microscopic evidence of tuberculosis. Animal inoculations were not made.

### II. BRONCHIAL LYMPH NODES ONLY INVOLVED

In one subject, 8 months old, several nodes at the root of the right lung showed tubercles with cheesy degeneration. No other sign of tuberculosis was found in any organ, and the case was grouped as one due to inhalation, since the lung, like the intestine, may allow the tubercle bacillus to pass through without localizing there.

### III. LUNGS AND BRONCHIAL NODES INVOLVED ALONE

Thirteen cases of this kind were noted, in which the tuberculous process was limited to the lungs and bronchial nodes, all other organs being free. It has very naturally been our custom to group these as cases of inhalation tuberculosis, and the view of both Weichselbaum<sup>12</sup> and Weleminsky,<sup>13</sup> who look on all cases involving the bronchial nodes together with the lungs as of digestive origin (since the primary lesion in the mesenteric or cervical nodes may be in the lymphoid stage, demonstrable by animal inoculation only; or else even this may have entirely disappeared and the primary lesion be cured instead of latent) seems to me not only far-fetched and unnecessary, but, in the light of Gaffky's<sup>14</sup> studies, untenable. Moreover, Oettinger<sup>15</sup> has shown that, after feeding experiments, when bacilli have entered the blood or lymph stream by way of the intestine and mesenteric lymph nodes, other viscera, especially the liver and spleen, must contain bacilli as well as the lungs; and if, after such experiments, the lungs alone are involved, then infection did not take place by way of the circulation, but directly by aspiration.

12. Weichselbaum (A.): Ueber die Infektionswege der menschlichen Tuberkulose. Sechste, Internat. Tuberkulose-Konferenz, Vienna, Sept. 19-21, 1907, p. 11.

13. Weleminsky: Sechste Internat. Tuberkulose-Konferenz, Vienna.

14. Gaffky (G.): Zur Frage der Infektionswege der Tuberkulose, Tuberculosis, Berlin, 1907, vi, 437.

15. Pettinger: Die Disposition der Lunge zur Erkrankung an Tuberkulose, Ztschr. f. Hyg. u. Infektionskrankh., 1908, lx, 557.

Ostermann<sup>16</sup> concludes from his recent examinations of the hands of persons in infected dwellings that contact infection in human beings must not be overestimated and that aspiration tuberculosis is by far more common; it is also more rapid in its development. Reichenbach confirms the latter statement, showing that the results of the inhalation method of tuberculous infection are both more rapid and more severe, at the same time requiring smaller doses of tubercle bacilli than does the contact method of infection.

According to Heymann's<sup>17</sup> experiments, tubercle bacilli are found in the lungs and bronchial glands one hour after the inhalation of large doses.

Flügge's<sup>18</sup> experiments show that tubercle bacilli reach the lungs very slowly by way of the intestinal tract and that relatively very large doses of tubercle bacilli are required to cause infection by way of the intestine, while exceedingly small numbers will, in the moist state, cause pulmonary tuberculosis when inhaled, as previously proved by Findel.<sup>19</sup> Since, as Most<sup>20</sup> and Beitzke<sup>21</sup> have shown, anatomically the tracheo-bronchial lymph nodes are not connected with the cervical lymph nodes, on the one hand, or with the abdominal lymph nodes, on the other, secondary infection of the bronchial nodes is possible only by way of the blood stream after the abdominal lymphatics have emptied their tubercle bacilli into the thoracic duct, or a blood vessel, in the process of degeneration of the nodes, has been entered directly.

Gaffky<sup>14</sup> examined the bronchial and mesenteric lymph nodes obtained at 300 autopsies on children up to 13 years of age, inoculating the nodes into guinea-pigs and then testing the isolated tubercle bacilli for their bovine or human type. Thirty-six cases were microscopically tuberculous, of which 27 were proved to be so by inoculation experiments. In 17 of these both mesenteric and bronchial glands were af-

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16. Osterman (A.): Die Bedeutung der Kontakt infection für die Ausbreitung der Tuberkulose, namentlich im Kindesalter. *Ztschr. f. Hyg. u. Infektionskrankh.*, 1908, ix, 375.

17. Heyman (B.): Versuche an Meerschweinchen über die Aufnahme inhalierter Tuberkelbacillen in die Lunge. *Ztschr. f. Hyg. u. Infektionskrankh.*, 1908, ix, 490.

18. Flügge (C.): Aetiologie der Tuberkulose, Sechste Internat. Tuberkulose-Konferenz, Vienna, Sept. 19-21, 1907, p. 46.

19. Findel (H.): Vergleichende Untersuchungen über Inhalations und Fütterungstuberkulose. *Ztschr. f. Hyg. u. Infektionskrankh.*, 1907, lxii, 104.

20. Most (A.): Die Topographie der für die Infektionswege den Lungen-tuberkulose massgebenden Lymphbahnen, Sechste Internat. Tuberkulose-Konferenz, Vienna, 1907, p. 132.

21. Beitzke (H.): Neuere Arbeiten über die Infektionswege der Tuberkulose. *Berl. klin. Wchnschr.*, 1908, xlv, 1225.

feeted, in 5 only the bronchial nodes, and in 5 only the mesenterics. In 30 other cases tubercle bacilli were found, 6 in the mesenterics, 12 in the bronchial nodes and 12 in both. In these 57 cases the bovine type of tubercle bacillus was found only twice and then in the bronchial and not in the mesenteric nodes. From his work Gaffky concludes that it is the human and not the bovine type of tubercle bacillus which is dangerous for children.

#### IV. PULMONARY OR BRONCHIAL LYMPH NODE LESIONS OR BOTH AS THE MOST ADVANCED LESIONS IN A GENERALIZED TUBERCULOSIS

These cases may be subdivided into two classes:

1. *The Tuberculosis in the Lymph Nodes More Advanced than that in the Lungs.*—In 25 cases the pulmonary tuberculosis was of the acute miliary variety, but the bronchial lymph nodes and the mesenterics both showed such marked cheesy degeneration that it was not possible to decide macroscopically or microscopically as to the comparative age of the two. In 3 others the mesenteric nodes were cheesy, though no intestinal ulceration had occurred. In 8 cases there were normal intestines and mesenterics, though liver and spleen contained tubercles. These were grouped unhesitatingly as of pulmonary origin, and one case with intestinal ulcers but unchanged mesenterics was looked upon as a secondary intestinal infection from swallowed sputum.

2. *Tuberculosis in the Lung the Oldest Lesion.*—In 83 cases of generalized tuberculosis in which the lungs were the seat of cheesy nodules, cheesy pneumonia, or cavity formation, the mesenteric lymph nodes were cheesy as well as the bronchial nodes and ulcers were present in the intestines. Twenty-six subjects had normal mesenterics and intestines, 5 had cheesy mesenterics without intestinal lesions, and 5 had normal mesenterics with ulcers in the intestines. Again the probable inhalation cases predominated.

#### V. INTESTINES AND MESENTERIC LYMPH NODES ALONE INVOLVED

But one such case occurred. It was that of a boy 22 months old. Twelve tuberculous ulcers were found in the jejunum and ileum, only one involving the peritoneal coat and undergoing cicatrization. But four ulcers were recent. The mesenteric nodes were all enlarged and the majority contained tuberculous areas. No other tubercles were found at autopsy, but on microscopic examination the spleen showed very recent ones within the Malpighian bodies. From the mesenteric

nodes of this subject Dr. Alfred F. Hess<sup>22</sup> isolated tubercle bacilli of the human type.

#### VI. INTESTINAL AND MESENTERIC LESIONS AS THE MOST ADVANCED OF A PARTIALLY GENERALIZED TUBERCULOSIS

There were five such instances:

1. *Boy, 2 Years Old.*—A tuberculous ulcer in the Peyer's patch above the ileocecal valve extended to the peritoneal coat, to which a cheesy lymph node was adherent; two other younger ulcers were in the ileum; all mesenterics were swollen and the majority contained cheesy tubercles. A few tubercles in the pia mater over both cerebral hemispheres were the only other evidence of tuberculosis in the body.

2. *Boy, 2 Years Old.*—One early tuberculous ulcer in the ileum and two in the cecum. Most of the mesenterics contained cheesy tubercles; one had become softened; miliary tubercles in pia mater, liver and lower lobe of right lung; bronchial nodes not tuberculous.

3. *Boy, 14 Months Old.*—One ulcer in the jejunum involved the peritoneum; two in the ileum; the majority of the mesenterics were cheesy and one had broken down; there were recent tubercles in spleen and liver.

4. *Boy, 11 Months Old.*—There were two recent tuberculous ulcers in the jejunum and two healing ones in the ileum; several solitary follicles in the cecum were cheesy. Many mesenteric lymph nodes contained cheesy tubercles, and one a calcareous area. One bronchial node showed a small, calcareous spot, and another showed several cheesy tubercles. A two-fold origin, by aspiration and by ingestion, seems to be the only rational explanation in this case.

5. *Boy, 1 Year Old.*—The patient was admitted with stomatitis and discharging (operation) wound over the left submaxillary gland. There was no history of tuberculosis in his family. All the cervical lymph nodes became enlarged; the stomatitis and gingivitis were very severe; pulmonary signs only ten days before death. At autopsy all the cervical nodes were found to have undergone cheesy degeneration, and the left submaxillary gland contained cheesy areas. Miliary tubercles were present in both lungs, liver, spleen and omentum; nine tuberculous ulcers in the jejunum and ileum; tubercles in the bronchial and mesenteric lymph nodes, but no large areas of cheesy degeneration. This may be looked on as a case of deglutition tuberculosis. The ingested bacilli af-

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22. Hess (A. F.): Primary tuberculosis of the mesenteric glands. Report of infections with bacilli of the human type. *Am. Jour. Med. Sc.*, 1908, cxxxvi, 183.

fecting the submaxillary gland and the cervical lymph nodes by way of the lymphatics of the mouth and pharynx and the intestines and mesenterics by being swallowed. Generalization by the blood current resulted from both the cervical and the mesenteric nodes, and hematogenous infection of the lungs and other viscera followed. That the tonsils and gums were not examined in this case is a matter of great regret.

#### VII. INTESTINAL AND MESENTERIC LESIONS AS THE MOST ADVANCED IN A COMPLETELY GENERALIZED TUBERCULOSIS

Only two cases occurred in this series in which the intestinal lesions were so extensive and advanced that the possibility of their being the oldest of a completely generalized tuberculosis presented itself.

It is evident that in my entire series of 185 cases there were but six, or 3.25 per cent., which may be positively classified as primary intestinal tuberculosis. Only one affected an infant less than 1 year of age. Bovaird,<sup>23</sup> in 1901, found that American statistics showed only 1 per cent. of primary intestinal tuberculosis against 4 per cent. of German cases and 18 per cent of English.

Medin<sup>24</sup> found, among 595 autopsies on tuberculous infants under 1 year of age, but six cases of primary intestinal tuberculosis, while in 273 the tuberculous process involved the lungs and bronchial lymph nodes alone. German authorities as a rule agree that cases of primary intestinal infection in infants and young children are rare. Hamburger<sup>5</sup> found no case among 335 autopsies on tuberculous children. Heller<sup>25</sup> is an exception, having found primary intestinal infection in 30.63 per cent. of his cases. English statistics on this subject are also high, Still<sup>26</sup> reporting 29 per cent. Fürst<sup>27</sup> estimates that about 160 cases of primary intestinal tuberculosis have been reported, including both adults and children.

No case in my series showed involvement of the mesenteric lymph nodes as the only evidence of tuberculosis at autopsy. In eight instances

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23. Bovaird (D. Jr.): Primary intestinal tuberculosis in children; its frequency and the evidence of its relation to bovine tuberculosis. *Arch. Pediat.*, 1901, xxviii, 881.

24. Medin (O.): Die Furch vor der Uebertragung der Tuberkulose und die Kinder durch die Kuhmilch ist unbegründet Sechste Internat. Tuberkulose-Konferenz, Vienna, 1907, p. 120.

25. Heller (A.): Ueber die Tuberkuloseinfektion durch den Verdauungskanal. *Deutsch. med. Wchnschr.*, 1902, xxviii, 696.

26. Still (G. F.): Tuberculosis in childhood. *Practitioner*, London, 1901, xiv, 91.

27. Fürst (L.): Die Intestinale Tuberkulose-Infektion mit besonderer Berücksichtigung des Kindesalters, Stuttgart, 1905, Ferdinand Enke.

the mesenterics had undergone cheesy degeneration without the presence of ulcers in any part of the intestinal tract. In all of these there were marked pulmonary and generalized tuberculosis, and the initial lesion, according to Weichselbaum,<sup>12</sup> Weleminsky,<sup>13</sup> von Behring<sup>28</sup> and Calmette,<sup>29</sup> may be assumed to be in the mesenteric lymph nodes.

The ulcers in the intestines were found to be most frequent and most advanced in the lower ileum, especially in the last Peyer's patch above the ileocecal valve. Ulcers were found above this point more often than below it, being present in the jejunum and ileum more frequently (in 35 instances) than in the ileum and cecum (in 28 instances). The jejunum, ileum and cecum were involved in 14 cases. The two ends of the intestinal tube were scarcely involved at all, ulcers being found in the rectum but twice and in the duodenum four times, but never alone. The gastric ulcers noted in 4 cases were superficial only. Geipel<sup>30</sup> also describes gastric ulcers in 6 of his cases as superficial and not confluent.

In the kidneys young miliary tubercles were found in 67 cases, almost always in both organs. The tubercles were in the main few in number and localized in the boundary zone between the cortex and medulla, or in the cortex beneath the capsule; in either case of hematogenous origin. Very small conglomerate cheesy tubercles were found in 5 cases, but again they were in the boundary zone and encroached on both cortex and medulla. The calyces and pelvis were invariably free from tuberculous infection.

The pulmonary lesions varied much, there being recent, discrete, miliary tubercles; conglomerate tubercles forming cheesy nodules of smaller and larger size, sometimes peribronchial in distribution; larger areas of cheesy pneumonia with or without cavity formation due to softening. Sometimes all these varieties were found in the lungs of a single subject. The oldest lesion in the lung was found on the right side in 95 cases, on the left in 66, and equally in both lower lobes in 3. The right upper lobe was involved rather more often than the middle or lower lobes. The lungs were free from tuberculosis in only 7 instances.

Cavity formation was noted in 39 cases, 6 involving more than one lobe. The cavities occurred more often on the right (in 26 instances) than in the left lung (in 19 instances), and more often in the upper and middle than in the lower lobes.

28. Von Behring (E.): *Leitsätze betreffend die Phthysiogenese beim Menschen und bei Thieren*. Berl. klin. Wchnschr., 1904, xli, 90.

29. Calmette (A.) and Guérin (C.): *Origine intestinale de la tuberculose pulmonaire*. An. de l'Inst. Pasteur, Paris, 1905, xix, 601; 1906, xx, 353.

30. Geipel (P.): *Ueber Säuglingstuberkulose*. Ztschr. f. Hyg. u. Infektionskrankh., 1906, liii, 1.

In the case of the bronchial lymph nodes the largest were found on the right side in 97, on the left side in 34 cases. This preponderance of the right over the left-sided pulmonary and bronchial lymph node tuberculosis is attributable to the purely mechanical fact that the right main bronchus is slightly shorter and bends away from the trachea less than does the left; therefore aspiration is facilitated in the direction of the right lung.

The mediastinal lymph nodes were markedly affected in 38 cases, the cervical in 6 and the retroperitoneal in an equal number. While caseation was the rule in all these variously situated lymph nodes, and suppuration was more common in the bronchial than in the mesenteric nodes, calcareous change was found but once in a mesenteric and five times in a bronchial lymph node, showing that the tendency of the tuberculous process in the lymph nodes of these young children is toward progressive degeneration rather than toward healing. Geipel<sup>30</sup> also found calcareous deposits unusual in the tuberculous lesions of infants.

#### SUMMARY

In this series of 185 cases showing tuberculosis at autopsy there were 13 in which the tuberculous lesions were limited to the respiratory tract, and only 1 involving the intestines alone. The point of entrance for the tubercle bacillus in these 14 cases was clearly in the lungs 13 times and in the intestinal tract once.

Four additional cases were of undoubted intestinal origin, 40 of respiratory origin and 1 of mixed respiratory and intestinal infection.

In the more advanced generalized cases 10 were possibly of intestinal origin, including 8 in which the mesenteric lymph nodes were involved without a tuberculous lesion of the intestines.

In the majority of cases of extensively generalized tuberculosis in young children the exact point of entrance must remain in doubt. Although the lungs were involved more frequently than any other organ (in 96 per cent. of all cases), this proves their marked predisposition to tuberculosis rather than their primary infection.

This study shows how comparatively rare undoubted cases of intestinal tuberculosis were in this series of infants and children under 3 years of age; and how, even when due allowance has been made for all doubtful cases, tuberculosis of respiratory origin predominated over that due to ingestion of the bacillus in these subjects.

TABLE.—LOCALIZATION OF LESIONS IN INDIVIDUAL ORGANS

Organs Affected.	Lesions.
Pia Mater.....	Tubercles only, 21; tubercles and inflammatory exudate, 44.
Brain.....	Solitary tubercle, 5, largest in right Sylvian fissure; 3 in occipital, 1 in frontal.
Pleura.....	Tubercles, 60; with empyema, 9; with bloody serous fluid, 10; chronic pleurisy, 29; acute fibrinous, 39.
Lung.....	Miliary tubercles only, 41; miliary tubercles and cheesy nodules, 54; cheesy pneumonia, 51; cavities, 39.
Pericardium.....	Tuberculous pericarditis at base, with one tubercle on pulmonary artery, 2.
Liver.....	Tubercles, 157.
Spleen.....	Tubercles, 161.
Stomach.....	Ulcers, single in 3; double in 1; all superficial.
Duodenum.....	Ulcers, with jejunum, 1; with ileum, 1; with ileum and cecum, 1.
Jejunum.....	Ulcers alone, 7; with ileum, 35; with colon, 2; with ileum and cecum, 14.
Ileum.....	Ulcers alone, 21; with jejunum, 35; with cecum, 24; with colon, 3; cheesy sol. fol., 1.
Cecum.....	Ulcers alone, 5; with ileum, 24.
Colon.....	Ulcers, with jejunum, 2; with ileum, 3.
Rectum.....	Ulcers, 2, with ileum.
Pancreas.....	Cheesy masses, 4.
Suprarenals.....	Tubercles, 5; microscopic only, in 1.
Kidneys.....	Tubercles, 67; small cheesy masses, 5.
Thymus.....	Tubercles, with cheesy degeneration, 5.
Submaxillary.....	Tubercles, with cheesy degeneration, 1.
Bronchial nodes...	Tubercles, with cheesy degeneration, 147; suppuration, 24; calcareous degeneration, 5.
Mesenteric nodes..	Tubercles, with cheesy degeneration, 131; suppuration, 3; calcareous degeneration, 1.
Cervical nodes....	Tubercles, with cheesy degeneration, 6.
Retroperitoneal nodes.....	Tubercles, with cheesy degeneration, 6.
Mediastinal nodes..	Tubercles, with cheesy degeneration, 38.

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## PRIMARY PORTAL THROMBOSIS

A STATISTICAL AND EXPERIMENTAL STUDY, WITH REPORT OF A CASE

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Thrombosis of the portal vein or its radicles is not uncommon as the terminal event in the clinical course of a number of different lesions affecting the abdominal viscera and vessels.

Lissauer<sup>1</sup> found that portal thrombosis occurred 68 times among 26,687 cases which came to autopsy at the University of Breslau. In 6 of the 68 cases the thrombosis was associated with atrophic cirrhosis of the liver; in 7, with syphilis of the liver; in 2, with primary carcinoma of the liver; in 7, with carcinoma of the stomach, accompanied by metastatic growths in the liver; in 2, with secondary carcinoma of the liver; in 6, with primary carcinoma of the biliary passages; in 9, with gallstones and inflammatory lesions of the gall bladder; in 10, with diseases of the pancreas; in 1, with suppurative inflammation of the umbilical vein; in 6, with diseases of the spleen; in 6, with gangrenous appendicitis; in 2, with carcinoma of the intestines; in 1, with a pelvic abscess, and in 3, with no definite cause.

In most of these cases of so-called secondary thrombosis the symptoms associated with the primary lesion have so masked those associated with the thrombosis that the latter has been overlooked entirely, clinically, or has been regarded as merely probable.

Primary thrombosis of the portal vein or its radicles is rare. Under this term are grouped those cases of thrombosis of the portal vein or its radicles which have occurred independently of any lesion of the abdominal viscera or vessels, not including, of course, those of the portal system.<sup>2</sup> There are a few cases in which the primary lesion in the intestine or adjacent lymphatic nodes have given rise to no symptoms, and in which the character of the clinical picture has depended entirely on occlusion of the portal vein or its radicles. These cases will be included in this paper.

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1. Lissauer (L.): Beitrag zur Frage der Entstehung der Pfortader-Thrombose. *Virchow's Arch. f. path. anat.*, 1908, cxcii, 278.

2. The cases observed by Greenough, Codman and Maclaure and Jacoulet have not been included. They were probably cases of primary portal thrombosis, but as autopsies were not held the possibility of primary lesions in other organs or vessels can not be excluded.

Talke,<sup>3</sup> in 1903, collected from the literature 8 cases of thrombosis of the portal vein or its mesenteric radicles which had been operated on. Up to the present time, including the case about to be discussed, 21 cases have been reported, in which an operation has been performed and a thrombosis of the portal vein or its radicles demonstrated at the operation or subsequent autopsy.

#### ETIOLOGY

The average age of the seventeen patients whose age is mentioned is thirty-seven and one-half years. The youngest patient was twenty years old, the oldest sixty-five. The lesion occurred eleven times in the male, six times in the female sex. In four cases neither age nor sex is mentioned. Nothing definite can be said concerning the direct cause of the thrombosis. The relationship between the previous illnesses, between the conditions found at operation or autopsy and the thrombosis must be regarded as assumed rather than proved. The patient operated on by Elliot<sup>4</sup> had a hernia, which had become incarcerated, but the hernia had been reduced ten months before the beginning of the symptoms due to portal thrombosis and had given no trouble in the meantime. Traumatism of the portal vein with subsequent thrombosis can certainly be excluded in this case. Frank's<sup>5</sup> patient had varicose veins and ulcers on the lower extremities. One of Köster's<sup>6</sup> patients had had, some years before the portal thrombosis, a severe diarrhea which had persisted for some time, while another patient observed by him had had typhoid fever two months before. The patient observed by Kölbing had had typhoid fever some years before, but gave no history suggesting a subsequent thrombophlebitis. One of the patients operated on by Garré<sup>7</sup> gave a history of a spontaneous thrombosis of the veins of the right thigh three years before the beginning of the portal thrombosis. In one of the cases observed by Sprengel<sup>8</sup> a definite history of thrombosis of one of the large veins of the left upper extremity could be elicited, and at the autopsy the left subclavian vein was found to be occluded at its junction with the jugular.

3. Talke (L.): Ueber Embolie und Thrombose der Mesenterialgefäße. Beitr. z. klin. Chir., 1903, xxxviii, 743.

4. Elliot (J. W.): The operative relief of gangrene of the intestine due to occlusion of the mesenteric vessels. Ann. Surg., 1895, xxi, 9.

5. Cited by Elliot: Ann. Surg., 1895, xxi, 9.

6. Köster (H.): Zur Casuistik der Thrombose und Embolie der grossen Bauchgefäße. Deutsch. med. Wchnschr., 1898, xxiv, 325.

7. Reported by Talke: Beitr. z. klin. Chir., 1903, xxxviii, 743.

8. Sprengel: Zur Pathologie der Circulationstörungen im Gebiet der Mesenterialgefäße, Arch. f. klin. Chir., 1902, lxxvii, 587.

It has been suggested that in cases such as those described by Garré and Sprengel there might exist a predisposition to endophlebitis and thrombus formation. The frequency with which a history of a preceding enterocolitis or an infection such as typhoid fever could be elicited in these cases is rather striking. No blood cultures were taken in the cases mentioned above and no bacteriologic examinations of the thrombus were made. The bacteriologic findings in the case observed by us seem to show that bacteria may circulate in the blood for a long period after the patient's convalescence from the original illness and produce later lesions, such as a pylephlebitis. It seems probable that a number of the cases of so-called primary pylephlebitis may be regarded as the sequelæ of enterocolitis which permitted the invasion of the radicles of the portal vein by bacilli of the colon group and healed before the symptoms resulting from occlusion of the vein developed. We believe that the case observed by us may be regarded as one of metapneumonic pylephlebitis, the involvement of the portal vein occurring five months after an attack of pneumonia. One of the cases observed by Köster should probably be regarded as a posttyphoid complication, thrombosis of the portal vein occurring two months after an attack of typhoid fever. The case observed by Bradford has been placed in this group because the clinical picture depended on the closure of the portal vein. In the case observed by him a suppurating mesenteric lymph node rested on one of the radicles of the vein, which later became involved.

The length of duration of symptoms is quite striking in some cases. Elliot's patient had complained of some abdominal pain for fourteen days. Then while he was playing ball the pain became excruciating and within twenty-four hours the symptoms of ileus were well marked. The development of the symptoms may be illustrated by citing in detail the case observed by us.

#### AUTHORS' CASE

*History.*—The patient, A. H. B., aged 38, was referred to us by Dr. Rikli of Naperville, Ill. He was taken sick April 30, 1908, with severe, cramp-like pains in the epigastrium. The pain developed suddenly and spontaneously while the patient was at work. It lasted but a few moments and then ceased, leaving no discomfort. Pain, similar in character to that just described, recurred the following morning at 7 and 11 and in the afternoon at 4. It had now become so severe that the patient was compelled to go to bed. A diagnosis of gastralgia was made at this time. The pain recurred the following morning. Two days after the beginning of the illness a stomach tube was passed and gastric lavage performed. Examination of the gastric juice, made at this time, revealed an absence of hydrochloric acid, a trace of blood, and shreds of gastric mucous membrane. The pains still recurred at intervals of from two to three hours and lasted from fifteen to thirty minutes. They were cramp-like in character and were most severe in the epigastrium, not radiating to any extent. Morphin was now re-

quired to control the pain. The patient did not vomit during the attacks of pain until after admission to the hospital. The bowels moved freely after the administration of cathartics. When admitted to the hospital on the morning of May 6, 1908, the patient was suffering paroxysmal attacks of pain such as accompany an obturation ileus.

*Examination.*—Temperature was 100.4 F.; pulse, 92 to 112; respiration, 28; leucocytes, 21,600. A history of pneumonia five months before and of slight gripping pain in the epigastrium six weeks ago could be elicited. The patient had been enjoying good health up to the beginning of present illness. It was thought at the time of the patient's admission that he might be suffering from perforation of a gastric ulcer. An ulcer could be excluded by the previous history. There were no distinct symptoms of peritonitis. As there were no indications for immediate operative interference, it was thought best to keep the patient under observation. When seen at night the abdominal distention, which had been noted in the morning, had become more marked. There was considerable epigastric tenderness and the muscles were distinctly rigid. The pulse had become rapid and wiry and the patient complained of paroxysms of agonizing epigastric pain. The clinical picture was suggestive of a paralytic ileus associated with an acute pancreatitis or an ileus accompanying an atypical appendicitis.

*Operation.*—As the condition of the patient had become much worse, it was thought best to perform an exploratory laparotomy. Because of the distention and tenderness in the epigastrium a mid-line incision was made midway between the umbilicus and xiphoid appendix. As soon as the peritoneum was opened a black loop of intestine two feet in length was found extending from above and to the left downward and to the right. There was no volvulus; there were no constricting bands, and as the patient had an aortic systolic murmur it was thought that the lesion was the result of embolism of the superior mesenteric artery. The infarcted loop was resected and an end-to-end anastomosis made.

The patient died after twelve hours, the gangrene having extended downward and having involved three feet of the intestine beyond the point of resection.

#### AUTOPSY

*Anatomic Diagnosis.*—Recent laparotomy with resection of part of the small intestine, serofibrinous peritonitis, thrombophlebitis of the portal vein with secondary thrombosis of the superior mesenteric and splenic veins; gangrene of the small intestines with rupture; acute mesenteric and retroperitoneal lymphadenitis; acute splenitis; cloudy swelling of the liver, kidneys and myocardium; localized bilateral fibrous adhesive pleuritis; slight sclerosis of the thoracic aorta; occlusion of the vermiform appendix; healed tuberculosis of the apex of the left lung.

*Visceral Cavities.*—When the body was opened there was found a large amount of turbid, bloody fluid in the peritoneal cavity. A large black loop of bowel, adherent to the omentum above and the bowel below, lay across the middle of the abdominal cavity. This loop of gangrenous bowel was the distal portion of a sutured piece of small intestine. The anastomosis was made 5 cm. from the point at which the duodenum pierced the root of the mesentery. The gangrene extended downward three feet from this point. The line of demarcation from the normal intestine was well defined. On the anterior surface of the gangrenous loop was seen a longitudinal tear through which intestinal contents exuded. The mesenteric lymph nodes were large and soft. The appendix was short and lay free with a mesentery of its own, 5 cm. in length. Within the pericardial cavity was seen a small amount of clear fluid. The pleural cavities contained no fluid. The lower part of the left and the upper part of the right cavity were wholly obliterated by adhesions. The tracheobronchial lymph nodes were not enlarged.

The heart was normal in size and its cavities were not enlarged. The myocardium was of normal color and consistency, but very friable; the endocardium was smooth throughout. The valves were unchanged.

*Superficial Examination of Organs.*—Spleen: The spleen was large, weighing 440 grams. Its surface was smooth. It was tense and of soft consistency. On the cut surface it had a grayish red color. The pulp was markedly swollen, but neither the Malpighian bodies nor the trabeculae were unusually prominent. The splenic artery appeared normal, but the splenic vein was filled throughout with an adherent, dark red clot. The stomach was normal in size and the pyloric opening was of normal caliber. The mucous membrane was smooth throughout and the rugae were prominent; the superficial veins along the greater and lesser curvatures were filled with dark, soft clots of blood.

Intestines: The lining of the duodenum was smooth and contained no areas of necrosis. The jejunum and ileum contained dark bloody fluid but no areas of necrosis. The mucous membrane of both these portions of the intestine was reddish black in color and was necrotic throughout. The mucous membrane of the large intestine was smooth throughout, but in the ascending colon it had a dark color.

The intima of the superior mesenteric artery and its branches was smooth and the vessels contained no clots. The superior mesenteric vein and all of its branches were filled with dark red clotted blood.

Liver: The liver was of normal size and appearance. It was soft in consistency. On cut surface it had a light grayish brown color. The portal vein and its branches within the liver contained soft red clots of blood. The intima in these places, where the caliber of the vessel was that of a slate-pencil or a little larger, was considerably roughened.

There were no changes in the gall bladder.

The pancreas appeared hyperemic; otherwise it was normal. The bladder, prostate and seminal vesicles, also the testicles, were unchanged.

The kidneys were of normal size. The capsule stripped with difficulty, but on cut section the kidneys appeared normal. Both kidneys were pale in color and friable.

The adrenals were unchanged.

*The Organs on Dissection.*—Heart: The pericardium was greatly thickened and the cavity partially obliterated by firm and more easily separable adhesions. The endocardium showed no change except several small grayish areas, one at the base of the posterior leaflet of the mitral valve, 2 mm. long by 1 mm. broad and 1 mm. thick. The other area of about the same size was in the anterior leaflet 3 mm. from its free margin. They were smooth on the surface and covered by endothelium. They presented the appearance of a beginning endocarditis of haematogenous origin.

In the aorta about 1 cm. from the aortic valves were several small, rough circumscribed, slightly elevated areas presenting the picture to the naked eye of ulcers.

The coronary arteries were smooth.

Liver: The liver appeared normal except for small elongated whitish areas, which radiated toward the center. One of these measured 1 by 1.5 by 2 cm. On dissecting the liver by opening the radicles of the portal vein we came to whitish thrombi, which extended from the smaller veins into the larger ones for a variable distance; the longest was 5 mm. They were adherent to the inner lining and were composed of an enormous number of leucocytes, much fibrin and many Gram-positive diplococci. Several of the whitish areas when opened contained a thick pus. A probe could readily be passed from this cavity into the larger branches

of the portal vein, thus showing that the whitish areas were really dilated and thickened radicles of the portal vein and not abscesses.

The peritoneum was smooth throughout. No lesion could be made out at site of subcutaneous injection.

Kidneys, spleen and lungs showed no change.

#### BACTERIOLOGIC REPORT

Stained smears of the heart blood showed no micro-organisms. Cultures on blood-agar plates, in strontiumcarbonate-glucose-free-dextrose broth, and in milk yield a pure culture of a Gram-positive diplococcus.

Portal vein blood smears showed a few Gram-positive diplococci and a fair number of Gram-negative short bacilli. Blood-agar plates showed a large number of colonies resembling the *Bacillus coli* and an average of fifty small colonies per 0.5 c.c. of blood surrounded by a greenish zone. These colonies on blood-agar plates were typical of those of the pneumococcus and were composed of the same Gram-positive diplococcus. This organism was also isolated on broth and milk. Cultures made from the portion of the thrombus which showed incipient softening in the portal vein within the liver gave similar results, except that the pneumococcus-like colonies were present in larger numbers. Bacilli resembling the colon bacillus were also isolated.

Smears and cultures from a mesenteric gland, the pericardial fluid and the bile proved to be negative, even on media especially favorable to the growth of the pneumococcus.

A small portion of the bloody intestinal contents contained in the gangrenous loop of bowel was plated out on blood-agar and plain agar plates. A pure culture of the *Bacillus coli communis* was isolated.

Further study of the Gram-negative moderately motile bacillus proved it to be the *Bacillus coli communis*.

The Gram-positive diplococcus, isolated in pure culture from heart blood and in conjunction with the colon bacillus from the blood in the portal vein and the thrombus was found on further study never to cause hemolysis on blood-agar plates. A distinct, greenish halo forms around its small colonies. Subcultures from animals inoculated showed no hemolysis. The organism fermented inulin slowly when planted on litmus inulin agar. This property was lost after cultivation on blood-agar slants for two weeks. Colonies on blood-agar slants tended to adhere to the surface for several generations. The bacteria grew in clumps and short chains in broth, litmus milk and in the water of condensation of the blood-agar.

The growth on plain agar slants was very scant; the colonies did not coalesce. Litmus milk was acidified in twenty-four hours; almost decolorized and coagulated in forty-eight hours. A culture in plain broth to test its solubility by ox bile could not be obtained early. Two weeks later, when a growth was obtained, bile failed to dissolve the cocci.

The individual organisms were somewhat smaller than the ordinary pneumococcus obtained from the blood in cases of pneumonia. They did not possess demonstrable capsules and had a tendency to grow in short chains and clumps and in the fibrin clot when the blood was added to broth. After passing them through animals encapsulated lanceolate diplococci were demonstrated in the animal's blood, the tendency to become closely attached to the surface of blood agar as well as to form chains and clumps having disappeared. At the same time the virulence now was so great that animals died promptly after inoculation from overwhelming pneumococcemia as they do after inoculation with pneumococci from pneumonia.

The organism when first isolated was moderately and slightly more susceptible to phagocytosis by washed normal leucocytes in normal serum than in the patient's serum.

Normal defibrinated blood and normal human serum as well had a decided bacteriolytic effect, while the organism grew readily in the patient's serum.

Agglutination here was marked. Unfortunately it was not possible to test the effect of the patient's leucocytes on this organism.

#### ANIMAL EXPERIMENTS

No. 157.—Large Belgian hare. May 13, 1908, inoculated with twenty-four hours' blood-broth subculture of the pneumococcus (of the second generation) isolated from the heart blood; 10 c.c. injected intravenously, and 10 c.c. injected intraperitoneally and subcutaneously.

May 14: The animal seemed ill. Blood cultures made from right ventricle.

May 15: Average of 100 colonies per c.c. of blood on blood-agar plates. Organism in stained specimen and in subcultures resembled exactly those originally isolated from the case.

May 16: The animal seemed somewhat better. Blood cultures made.

May 18: The hare seemed somewhat better. Blood cultures negative.

May 24: The hare apparently was recovering; ate, but showed marked loss of weight.

May 25: The animal seemed fairly well but was still losing weight.

May 30: The hare seemed much worse. Large swelling on the right upper lip measuring 1.5 by 2 by 2 cm. Blood culture made from vein of ear.

June 1: Blood culture negative; swelling larger. The animal seemed worse.

June 2: Hare dead.

*Autopsy.*—Anatomic diagnosis: Acute osteomyelitis; adhesive and fibrinous pericarditis; incipient mitral and aortic endocarditis; descending thrombophlebitis portal vein.

The swelling in the left upper jaw was due to an osteomyelitis of maxilla. The pus from here was rich in leucocytes and Gram-positive diplococci. Cultures from the pus of upper jaw, blood and thrombi in the portal vein yielded pure cultures of pneumococci.

Another rabbit receiving an intraperitoneal injection recovered; autopsy two months later proved negative.

With the idea in mind that possibly the pneumococcus in this case might have gained access into the portal circulation by way of the hemorrhoidal vessels, although on close inquiry no history of rectal irritation could be elicited, I injected a large amount of a culture into the rectums of two guinea-pigs, one without, the other with injury to the mucous membrane. Both animals recovered and a month and a half later were chloroformed and examined with negative result.

Two guinea-pigs and one rabbit died of an overwhelming pneumococemia in twenty-four hours after inoculation with the organism isolated after death from Animal 157. The organisms now presented the features of the pneumococcus cultivated from patients suffering with pneumonia. They resisted phagocytosis, were encapsulated in the blood, and no longer grew fast to the surface of media upon which cultivated.

The animal experiments would seem to establish quite thoroughly the etiologic rôle which this organism must have played in the production of the thrombophlebitis. The susceptibility to phagocytosis, the mild virulence, the increased opsonic index of the serum, the marked growth and agglutination of the organism in the patient's serum, as well as the peculiar cultural and morphologic properties, which are lost

by cultivation on media and animal inoculation, all are in exact accord with similar observations made on strains of pneumococci isolated from cases of chronic septic endocarditis. These observations are not only interesting from the bacteriologic standpoint as illustrating environmental modification of bacteria, but are of great value in interpreting the pathogenesis in this and, we believe, in other similar cases of thrombosis.<sup>9</sup> After all, the pathology in this case is not so very different from that of endocarditis. In the former the endothelium of the heart, usually of the valves, is involved, while here the endothelium of the portal vein is the seat of the primary lesion; both are vascular endothelium and embryologically derived from the same structures. Indeed, the histologic structure of a vegetation in these cases of endocarditis is not very different from that of a thrombus, the former being richer in fibrin and bacteria and the latter in red blood corpuscles, as conditions are more favorable for coagulation.

#### LIST OF CASES FROM LITERATURE

CASE 1 (SACHS<sup>10</sup>).—*History*.—A man, aged 32, addicted to alcohol, had complained of abdominal pain for some time. He suddenly developed severe abdominal pain and intestinal hemorrhages; obstipation was marked and the vomitus soon became fecal in character. The abdomen became markedly distended. Exploratory laparotomy revealed several bluish-black loops of intestine and permitted the escape of large quantities of fluid with a fecal odor.

*Autopsy*.—Almost all of the small intestine was black; the stomach contained large amounts of a reddish fluid. The trunk of the portal vein was filled with a thick, dark-red clot, which extended downward into the superior mesenteric vein.

CASE 2 (ELLIOT<sup>4</sup>).—*History*.—The patient was a young man, aged 25, with an inguinal hernia which had become incarcerated ten months before, but had been reduced, causing no symptoms. He had had recurring abdominal pain for two weeks before the beginning of acute symptoms. While playing ball, he experienced sudden, severe abdominal pain. He began to vomit soon after and was taken to the hospital. The entire abdomen was tender; there were repeated attacks of colicky pain; no meteorism; a sausage-like mass was found in the ileocecal region.

*Operation*.—Large quantities of serohemorrhagic fluid escaped from abdominal cavity. Some dark-red, foul-smelling loops of intestines escaped. The inguinal rings were free and there was no volvulus. The mesentery was of normal length, but the vessels felt hard and were apparently thrombosed. The mesenteric lymph nodes were swollen. Forty-eight inches of empty intestinal loops, which were not distended, were resected. The vessels bled but little. Because of increasing shock the resected ends were sutured into the abdominal wound.

The resected ends were united fourteen days later, the patient making a recovery. The veins of the resected portion of the intestines were closed by thrombi.

9. Rosenow has isolated similar strains of pneumococci from the blood during life in a case of non-fatal thrombophlebitis of the left subclavian and innominate veins which developed during the puerperium; and after death in a case of fatal pulmonary embolism from thrombosis of the left internal iliac vein following appendectomy.

10. Sachs (R.): *Zur Casuistik der Gefässerkrankungen*. Deutsch. med. Wchnchr., 1892, xviii, 443.



CASE 3 (KENDAL FRANKS<sup>5</sup>).—A patient with varicose veins and ulcers developed symptoms of acute, intestinal obstruction. There was no discharge of gas or feces. At the operation a volvulus of some loops of the small intestine, which were gangrenous, was found. The mesentery corresponding to these loops was thick and edematous and all the veins were thrombosed. "The veins felt as cords running through the mesentery and apparently the lesion was not recent." Sixteen inches of the intestine were resected; end-to-end anastomosis with suture was done. Death occurred after two days.

*Autopsy.*—Some of the intestine below the point of resection had become gangrenous. The portal vein and the veins draining the gangrenous loops were filled with thrombi. Franks regarded the volvulus as secondary to the thrombosis.

CASE 4 (J. C. BLOODGOOD<sup>11</sup>).—*History.*—The patient, aged 52, had been a soldier. Three weeks before admission he had sudden abdominal pain, not very severe in character, associated with vomiting; since then intervals of moderately severe pain, chiefly in umbilical region, and vomiting; a few days before admission, acute abdominal pain in region of umbilicus, with vomiting. This attack was aggravated by the administration of cathartics on the next day. There was no passage of fecal matter, blood or flatus from this time. Three days before admission nothing was retained by the stomach; the abdomen was slightly tender above and to the right of umbilicus and moderately distended.

*Examination.*—On admission to the surgical wards of Johns Hopkins Hospital, Sept. 15, 1896, the patient was found excessively fat. Temperature was 100, pulse 72, respiration 24. Facies was typical of a severe intraperitoneal lesion. The abdomen was moderately distended; there was slight muscle spasm, but no tenderness. Palpation was difficult on account of thick abdominal walls. No mass was detected on palpation. Rectal examination was negative; there was no fecal matter in the rectum.

*Operation.*—Laparotomy was performed September 15 by Dr. Bloodgood. There was bloody fluid in the peritoneal cavity; no fecal odor. The movable mass proved to be omentum adherent to coils of small intestine beneath it. The mass was excised. About 8 cm. of a loop of ileum was gangrenous; the neighboring intestine was congested and covered with fibrin. There was no perforation, and no fecal extravasation. The mesentery seemed normal. The gangrenous loop of intestine was drawn out of the wound and the intestines drained by tubes inserted above and below.

*Postoperative History.*—After operation the patient vomited a great deal of bile-stained fluid. This vomiting continued intermittently during the next three days. On September 17 the gangrenous loop came away from the wound without bleeding. Temperature was 100.5; pulse 120. The pulse became very weak during the night and rose to 160. On September 18 the temperature was 103. Death took place at 10:30.

*Anatomic Diagnosis.*—Thrombosis of mesenteric veins, necrosis and gangrene of small intestines, general fibrinopurulent peritonitis. The main trunk of the portal vein was also filled with firm thrombi extending from that in the mesenteric vein.

CASE 5 (BRADFORD<sup>12</sup>).—*History.*—The patient, a man aged 20, complained at first of pain in the abdomen and some diarrhea. The diarrhea disappeared; then pain developed in the region of the navel and vomiting commenced. Physical examination revealed nothing in viscera. Respirations were somewhat rapid; pulse

11. Cited by Jackson (J. M.), Porter (C. A.) and Quinby (W. C.): Mesenteric embolism and thrombosis. Jour. Am. Med. Assn., 1904, xlii, 1469.

12. Bradford (R.): Thrombosis of superior mesenteric vein causing intestinal obstruction. Brit. Med. Jour., 1898, i, 1137.

about 96. Cathartics were administered without results. Vomitus became fecal in character and an indefinite mass could be palpated in the ileocecal region. The diagnosis of intestinal obstruction was made. As the patient rapidly grew worse a laparotomy was performed on the ninth day of illness. Thrombosis of the superior mesenteric vein was found. Death followed immediately after the operation.

*Autopsy.*—Intestines dark red in color, swollen, and gangrenous in some areas. Gangrene involved about eighteen inches. The mesentery was thickened. The superior mesenteric vein was filled with old, partly disintegrated thrombi, which extended into the portal vein. The clots occluding the latter were fresh. The superior mesenteric artery and its branches were normal. The mesenteric lymph nodes were enlarged and hemorrhagic. One had suppurated and the abscess cavity communicated with the interior of the thrombosed vein. The involvement of the vein was secondary to suppuration in the adjacent lymph node.

CASE 6 (KÖSTER<sup>13</sup>).—*History.*—A man, aged 31, had suffered with a persistent diarrhea some years before the beginning of the symptoms due to portal thrombosis. His last illness began without any apparent cause with severe pain in the region of the bladder, which soon extended over the entire abdomen. Simultaneously hiccoughing and vomiting, not fecal in character, developed. Neither gas nor feces were discharged, notwithstanding that enemas were given. There was tympanitic distention of the upper part of the abdomen, while the lower part was dull. Exploratory laparotomy revealed that the greater part of the intestine was gangrenous. Death took place on the following morning.

*Autopsy.*—There was a small amount of dark-red, cloudy, foul-smelling fluid in abdomen. The greater part of the descending colon was gangrenous, likewise the entire sigmoid flexure. None of the intestinal loops were collapsed. The entire peritoneum was smooth and shining, with the exception of that covering the gangrenous intestine. The mucous membrane of the small intestine was normal. In the ascending colon there were some swollen follicles. In the upper part of the descending colon, above the gangrene, was a lesion in the mucous membrane 3 cm. in length, which extended into the muscularis. The rectal mucous membrane was normal, likewise the aorta and mesenteric veins. The veins draining the gangrenous part, likewise the inferior mesenteric vein, were closed by adherent thrombi.

CASE 7 (KÖSTER<sup>13</sup>).—*History.*—A woman, aged 40, suddenly became ill two months after convalescence from typhoid fever. Symptoms consisted of abdominal pain and fecal vomiting. There was no improvement after enemas had been given and a laparotomy was performed. Adhesions between the omentum and the lower part of the ileum were found and freed; the symptoms of ileus then subsided. After the patient had remained well for six weeks, abdominal pain and vomiting again developed. The patient soon passed into collapse and died.

*Autopsy.*—There was gangrene of almost the entire small intestine, extending from close to the duodenojejunal angle to the ileocecal junction. The mesentery was considerably thickened and injected, and the veins in the same were filled with dark, firmly attached thrombi.

CASE 8 (C. A. PORTER<sup>14</sup>).—*History.*—The patient was a woman 38 years of age. She had had more or less chronic diarrhea for the last three or four years. She had had three children, the last, five weeks before entrance to the hospital. She was in bed ten days; her convalescence was normal. Her previous pregnancy was in 1897, after which she was in Massachusetts General Hospital for milk leg.

13. Köster (H.): Zur Casuistik der Thrombose und Embolie der grossen Bauchgefässe. Deutsch. med. Wchnschr., 1898, xxiv, 325.

14. Jackson (J. M.), Porter (C. A.) and Quinby (W. C.): Mesenteric embolism and thrombosis. Jour. Am. Med. Assn., 1904, xlii, 1469; 1904, xliii, 25.

*Present Illness.*—The patient had been well till January 21, when she had some pain in the right hypogastrium, not severe, but enough to prevent working. The pain soon moved to the umbilicus; it was colicky in nature, coming and going. The patient vomited in the evening before entrance. The bowels moved every day until the day of entrance; there was nothing peculiar about the stools. The pain gradually increased in severity. The patient entered the hospital at 7 p. m., Jan. 25, 1899. She had pain in the abdomen and poor pulse at 8 p. m. An enema brought away a few small fecal masses of normal color and consistency.

*Examination.*—At 9 p. m. temperature was 98.6; pulse 80, of poor quality; respirations, 23; leucocytes, 50,200. The woman was pale, rather poorly nourished, with hollow eyes with dark rings around them. The eye was clear; expression rather "pinched," though perfectly bright and intelligent; it was evident that she was laboring under peritoneal shock. Pain was most marked directly beneath the umbilical cicatrix; tenderness was greatest over an area the size of the palm of the hand, to the left of the umbilicus, where the muscles resisted the slightest pressure. There was dullness in left lower quadrant. No peristalsis was heard on auscultation. Vaginal examination: rather large uterus, not tender. Some induration without tenderness in left side of pelvis, no bulging. Rectal examination negative; urine: red color, acid, albumin 0.25 per cent., sugar absent; sediment contained some pus, considerable normal blood, a few granular casts and squamous epithelium from bladder or vagina.

*Operation.*—Directly below area of tenderness described above a coil of dull plum-colored bowel was found. An artificial anus was made after resection. Death took place the following day.

*Anatomic Diagnosis.*—Resection of intestines; extensive thrombosis of portal vein and its larger branches; hemorrhagic infarction of a portion of jejunum; acute degenerative nephritis.

CASE 9 (KÖLBING<sup>15</sup>).—*History.*—A woman, 31 years of age, was admitted to the hospital Sept. 20, 1901. She gave a history of typhoid fever three years before, but had been perfectly healthy since. She had been delivered July 24, 1901, but the puerperium had been perfectly normal and she had been discharged from the hospital in nine days. On Sept. 16, 1901, after a diarrhea had persisted for some days, a severe pain developed suddenly in the abdomen, which gradually grew worse. On the 19th and 20th vomiting, not fecal in character, developed and recurred frequently. On September 21 an enema was given, and small fecal masses with admixture of blood were returned. No gas was discharged. The abdomen became still more distended during the day. Vomiting recurred, and the temperature rose to 101.8 F. The patient was transferred to the surgical service.

*Examination.*—The lateral abdominal regions were greatly distended and somewhat tender; the umbilical region soft and not especially prominent. An intestinal loop, which on percussion gives a clear tympanitic note, could be traced from the ileocecal region to the liver and from here under the costal margin to the left. A similar loop was found on the left side, which extended upward to the region of the stomach. The vomitus had a fecal odor. A diagnosis of strangulation ileus was made.

*Operation.*—Laparotomy was performed. When the peritoneum was opened about a quart of clear fluid escaped under pressure. The exposed intestinal loops were injected, but not especially distended. The cecum and descending colon were collapsed. An infiltrated, resistant loop of intestine could be palpated in the region of the stomach. This loop could not be brought out of the abdominal cavity

15. Kölbing (P.): Beiträge zur Magendarmchirurgie. Beitr. z. klin. Chir., 1902, xxxiii, 518.

until the incision was prolonged above the umbilicus. It was then found that about twenty inches of the upper part of the jejunum was reddish-black in color, friable and gangrenous. The mesentery corresponding to this loop was hard, infiltrated and ecchymotic. It could be demonstrated, during resection of the loop of bowel, that the veins were closed by thrombi. After the gangrenous loops had been resected the proximal end of the intestine was invaginated and a gastro-enterostomy made between the stomach and distal end.

The patient made an uneventful recovery.

CASE 10 (PICQUÉ and GRÉGOIRE<sup>16</sup>).—The patient had diarrhea, without blood, which persisted for twenty days; then obstipation for three days, followed by bloody stools. It was thought advisable to perform an exploratory laparotomy, no definite diagnosis having been made. The findings revealed by operation warranted an artificial anus, even though the exact cause of the pathologic changes could not be determined. Autopsy revealed a thrombophlebitis involving the superior mesenteric vein with accompanying gangrene of the intestinal loops drained by it.

CASE 11 (PICQUÉ and GRÉGOIRE<sup>16</sup>).—The case was diagnosed as probably volvulus of the sigmoid. An exploratory laparotomy revealed gangrene of the intestine but no torsion or constricting bands were found. Autopsy revealed, as in the preceding case, a thrombophlebitis of the superior mesenteric vein which had extended to the portal.

CASE 12 (SPRENGEL<sup>8</sup>).—*History.*—The patient, a man aged 22, had been treated for gonorrhea earlier. No previous history was elicited which could have any etiologic relationship to the present trouble. He had been confined to bed for fourteen days with indefinite symptoms when pain suddenly developed in the epigastrium, which later radiated to the lower abdomen to the right of the urinary bladder. There had been no bowel movement for four days and no discharge of flatus. Vomiting was frequent and profuse. Vomitus consisted of a reddish brown material in which blood could be demonstrated. No blood was discharged by rectum. Exploratory laparotomy revealed extensive infarction of intestinal loops. Death soon followed.

*Autopsy.*—Veins draining the infarcted loops were closed by firm thrombi. Thrombi also extended into portal vein. Thrombi which were not firmly attached found also in pelvic veins.

CASE 13 (SPRENGEL<sup>8</sup>).—*History.*—An unmarried woman, 25 years of age, was admitted to the hospital because of a swelling, which she had noticed for ten weeks in the inguinal region. Three and one-quarters years previously a swelling of the left arm, supposedly due to a thrombosis of one of the large veins, had developed spontaneously. Swelling gradually subsided as an extensive collateral circulation developed in the subcutaneous veins of the chest. No history of any previous inflammatory lesion of the arms, neck or ear could be elicited. Three weeks after admission to the hospital the hernia which had been noted some ten months before was repaired. Convalescence was rapid, the patient being up and about in three weeks. One week later pain suddenly developed in the epigastrium. Two days later some resistance was noted about the umbilicus and a reddish fluid was discharged by rectum. There was no abdominal distention. On the following day there was fecal vomiting. A diagnosis of obturation ileus was made. Laparotomy revealed an infarcted intestine and about three feet of the same were resected. Death followed.

*Autopsy.*—There was occlusion of the left jugular and subclavian veins at junction. The main branch of the portal vein was closed by thrombi, but a col-

16. Picqué and Grégoire: Thrombo-phlébite de la veine mesaraïque supérieure, avec gangrène de l'intestin. *Semaine méd.*, 1902, xxii, 21.

lateral circulation had been established by large accessory vein passing up to liver. The exact nature of this collateral circulation could not be determined.

CASE 14 (GARRE<sup>17</sup>).—*History*.—A man, 61 years of age, was admitted to the Rostock surgical clinic July 8, 1898. He had suffered three years before with spontaneous thrombosis of right femoral vein. He was a moderate drinker. He had been in good health the year before the beginning of present trouble. On July 5 he was seized with general abdominal pain, with no preceding digestive disturbance. Vomiting of material without fecal odor commenced at about the same time that pain did. Neither gas nor feces expelled, notwithstanding that enemas were given frequently. On the following day vomiting ceased for sixteen hours but pain and hiccoughing persisted; no gas was expelled. On July 7 vomiting commenced again, the abdomen became distended, the pain increased, the patient became dyspneic and sank rapidly. No gas was expelled and no feces discharged. Urination was difficult. During transportation to hospital vomiting became fecal in character.

*Examination*.—The face was cyanotic and pinched; the pulse small, 140 and very soft; respirations very rapid. The extremities were cold, and the entire body covered with cold sweat. The sensorium was dulled. The heart was enlarged to the right, tones soft and *pure*. The abdomen was somewhat distended, the abdominal muscles were tense, and the entire abdominal wall tender. There could be palpated in the epigastrium an induration with a round upper border, which became broader below and became continuous with an indefinite resistance about the navel. No peristaltic waves were to be seen. The liver and spleen were not enlarged.

*Operation*.—A midline incision was made in the epigastrium extending two fingers' breadth below the navel. A reddish fluid with a fecal odor escaped when the peritoneum was opened. A gangrenous loop of bowel presented, which was adherent to omentum and neighboring coils. Four and a half feet of the intestine were resected and end-to-end anastomosis with Murphy button was made. Death took place seven hours after operation. Autopsy was refused. Examination of resected portion showed that the veins were dilated and filled with thrombi which extended into the vessels of the intestinal wall. Clots were laminated. The mesenteric arteries were narrow, but patent.

CASE 15 (STEPHAN<sup>18</sup>).—The patient was a man 65 years of age with all the symptoms of ileus; pulse, 118; temperature, 98. Laparotomy was performed. There was serohemorrhagic exudate in the peritoneal cavity. A gangrenous loop of bowel was resected and an end-to-end anastomosis made with a Murphy button. Death took place at the end of the operation. Autopsy showed thrombosis of the portal vein, extending into mesenteric radicles.

CASE 16 (LINDNER<sup>19</sup>).—A man aged 56, with negative previous history, had complained for eight days of some abdominal pain and vomiting. He had had obstinate constipation for three days with some distention of the abdomen.

*Examination*.—On admission to the hospital the patient's face was anxious, pinched and somewhat cyanotic. The abdomen was distended and tender; liver dulness was partially obliterated. The patient was hiccoughing. Two hundred and fifty cubic centimeters of non-fetid fluid were removed from the stomach by

17. Reported by Talke: Beitr. z. klin. Chir., 1903, xxxviii, 743.

18. Stephan (B. H.): Bijdrage tot de Casuistik de gevallen von acute Pfortader thrombose. Med. Weekbl., 1900, vi, 31.

19. Cited by Mauclair (P.) and Jacoulet (F.): Infarctus hémorrhagique de l'intestin par oblitération veineuse ou artérielle. Arch. gén. de chir., 1908, iv, 341.

the stomach-pump. Temperature was 98.6; pulse, 100. A diagnosis of peritonitis was made.

*Operation.*—A median laparotomy above the umbilicus was performed. A non-fetid, serosanguinolent fluid escaped after incision of the peritoneum. A black loop of the jejunioileum measuring about six feet in length was found, the walls of which were very thick. The segment of mesentery corresponding to this loop was edematous and very hard. An ecchymotic transitional zone was found at each end of the infarcted loop. Eight feet of the intestine were resected, an end-to-end anastomosis being made. Distention of the abdomen and vomiting continued and death took place twenty hours after operation.

*Autopsy.*—Thrombosis of portal vein. Hemorrhagic ulceration of stomach, thrombosis of mesenteric veins and inferior vena cava. Fatty degeneration of the pancreas; thrombosis of splenic vessels and splenic infarct. No leakage at point of anastomosis.

CASE 17 (BRÜNNER<sup>20</sup>).—*History.*—The disease began acutely with chills and vomiting, the patient having been apparently in good health. The abdomen was somewhat distended; no gas or feces were discharged. There was some elevation of temperature, and persistence of chills. Examination of the abdomen revealed a poorly defined mass situated to the left and below the umbilicus. A diagnosis of carcinoma of the descending colon was made. A laparotomy was done. An infarcted loop of small bowel measuring 12 cm. in length was resected with the corresponding segment of mesentery. Recovery followed. Examination of the specimen revealed a thrombosis of the mesenteric veins. Arteries were permeable.

CASE 18 (MONNIER and SUTER<sup>21</sup>).—A woman, 30 years of age, was brought to the hospital with symptoms of acute intestinal obstruction. Laparotomy was performed. There was a large amount of serosanguinolent fluid in the peritoneal cavity; gangrene of several loops of small intestine; thrombophlebitis of the superior mesenteric and portal veins. Death took place twelve hours after operation.

CASE 19 (MONNIER and SUTER<sup>21</sup>).—A woman 35 years of age suddenly developed the symptoms of acute intestinal obstruction three months after a phlebitis, involving both lower extremities. Laparotomy was done. Infarction of all of the lower loops of the ileum was found, with beginning gangrene. The veins of the mesentery were thrombosed. There was a serosanguinolent peritoneal exudate. A segment measuring two feet was resected. Death took place twenty-four hours after operation. Autopsy revealed thrombosis of the mesenteric veins and large systemic veins of abdomen.

CASE 20 (HAAGEN<sup>22</sup>).—The patient was a man, 37 years old. Symptoms began acutely. Laparotomy revealed an infarcted loop twelve inches in length. Anastomosis with Murphy button was done, and an operation three weeks later to free adhesions. Recovery ensued.

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20. Brünner (F.): Thrombose septique des veines mésentériques. Opération. Guérison. Soc. de méd. de Zurich, 1907. Cited by Maclaure and Jacoulet: L'infarctus hémorragique de l'intestin par oblitération veineuse ou artérielle. Arch. gén. de chir., 1908, iv, 361.

21. Monnier and Suter: Deux cas de thrombophlébite mésentérique. Soc. de méd. de Zurich. Cited by Maclaure and Jacoulet: L'infarctus hémorragique de l'intestin par oblitération veineuse ou artérielle. Arch. gén. de chir., 1908, iv, 361.

22. Haagen (T.): Mitteil über einen durch Operation geheilten Fall von Thrombose in Gebiete der Vena mesenterica superior. Deutsch. Ztschr. f. Chir., 1908, xcii, 19.

## SYMPTOMS AND DIAGNOSIS

The symptoms associated with thrombosis of the portal vein and its mesenteric radicles are similar to those following thrombosis of the mesenteric arteries. It is always difficult, often impossible, to make a diagnosis of circulatory ileus, and it is probably impossible to make a differential diagnosis between venous and arterial thrombosis. If, when the symptoms of ileus develop, a preceding history of an infection which not infrequently is accompanied by thrombophlebitis is elicited, a diagnosis could probably be made.

One of the most constant symptoms in these cases of primary portal thrombosis is pain. The pain is cramp-like in character, recurring at frequent intervals. The radiation of the pain is not typical, often extending within a few hours over the entire abdomen. In one case observed by Köster the pain in the beginning was general, but later settled in the region of the urinary bladder. The patient operated on by Elliot complained of recurring attacks of abdominal pain for two weeks before the beginning of the symptoms of ileus, which developed acutely. The patient observed by Bloodgood was seized with severe abdominal pain three weeks before an operation was performed. In this case it is probable that the pain was associated with the portal thrombosis, although when the autopsy was performed a peritonitis was found. In other cases only two or three days have intervened between the beginning of symptoms and death.

There may be complete obstruction to the passage of gas and feces or mucohemorrhagic diarrhea. The diarrhea with hemorrhage has been supposed to be in most cases the direct result of intestinal infarction. Quénu has made the highly interesting suggestion that in the cases in which there are frequent mucohemorrhagic discharges the lesion may be primary in the intestine; the lowered resistance of the intestinal wall in such cases permitting of bacterial invasion of the radicles of the portal vein.

The way in which the symptoms develop and the sequence which they follow are not at all characteristic. In almost all of the cases a diagnosis of ileus has been made and the nature of the ileus has been revealed by an exploratory laparotomy.

It is possible that a diagnosis of perforation of a duodenal ulcer might be made in these cases. The pain accompanied by blood in the feces and paralytic ileus make a symptom-complex which resembles quite closely that of circulatory ileus. A carefully elicited previous history would aid one in excluding duodenal ulcer.

## TREATMENT

The operation to be performed after the nature of the lesion has been determined depends altogether on the conditions found. In some cases (Köster, Sachs) the gangrene is so extensive that resection would be impossible. The fact that recovery has occurred in 4 cases makes it imperative that the limits of the gangrene be determined as accurately as possible and that the resection be made in healthy tissues. It is not always possible to determine the extent of the thrombosis or whether it is progressing or at a standstill. This is well illustrated by the case observed by us, in which the resection was carried well into healthy bowel and yet within twelve hours three feet of intestine beyond the point of resection had become gangrenous.

The large intestine is but rarely involved in gangrene due to venous thrombosis, for the communication between the hemorrhoidal and systemic veins seems to be extensive enough to provide for a return flow when the radicles of the portal vein are closed. The duodenum apparently is not involved in gangrene after portal thrombosis. The gangrene involves the upper intestinal loops, but does not extend beyond the point at which the duodenum pierces the mesentery. The collateral venous circulation in the "fascia of fusion" seems to be extensive enough to provide for the return of venous blood from the duodenum even when the main trunk of the portal vein is occluded.

Resection may be exceedingly difficult in these cases of portal thrombosis. The mesentery is thickened and rigid as a result of the edema; the two ends of the bowel may vary greatly in size; there is an ectropion of the intestinal mucous membrane; and the gangrene may extend so high that it is nearly impossible to use the proximal end of the intestine, as the anastomosis must be made at the point at which the duodenum pierces the root of the mesentery.

In the case reported by Kölbing (operation by Linder) the gangrene involved the upper loops of the small intestine. The resection was made so close to the root of the mesentery that it was impossible to make an end-to-end anastomosis. The end of the duodenum was, therefore, closed and invaginated at the point at which it pierces the root of the mesentery, the gastroenterostomy being made with the jejunum. After an operation of this type the pancreatic juice and bile must flow back into the stomach before it can escape through the gastroenterostomy orifice. The patient made an uneventful recovery. Moynihan had previously employed the same procedure in operating in a case of traumatic rupture of the intestine at the duodenojejunal angle. The patient recovered from the operation, but died 104 days later following



perforation of the duodenum by a Murphy button which had been employed in making the gastroenterostomy.

Some animal experiments made recently by Lewis would seem to indicate that in the majority of cases animals die after the duodenum is divided and invaginated and a gastroenterostomy made with the distal loop. These animals recover from the immediate effects of the operation, but soon begin to vomit, practically all the food being regurgitated. The animals live from thirty to forty days and die of inanition. When a postmortem examination is made, the duodenum is found to be enormously dilated, resembling the stomach. The food is apparently forced into the duodenum and then thrown back into the stomach without passing through the gastroenterostomy orifice. The animals die of disturbances of motility rather than of disturbances in chemical changes.

Four of the 21 patients recovered. Elliot, in the case reported by him, resected four feet of intestine and made an artificial anus, which was closed fourteen days later. In the case reported by Kölbing twenty inches of intestine were resected, the end of the duodenum invaginated and a gastroenterostomy performed with the jejunum. Brünner resected five inches, making an end-to-end anastomosis, while Haagen resected twelve inches, making a lateral anastomosis with a Murphy button.

#### CONCLUSIONS

1. A careful bacteriologic examination of the blood, using media which favor the growth of the highly parasitic bacteria, will, we believe, establish, as in the case reported by us, the etiologic rôle that bacteria play in portal thrombosis.

2. It is impossible to differentiate between thrombosis of the mesenteric arteries and veins, but a probable diagnosis of circulatory ileus can be made if the history reveals some previous illness which is frequently associated with inflammatory changes in the arteries and veins.

3. The procedure to be adopted depends altogether on the conditions revealed by the exploratory operation. A record of 4 recoveries in 21 cases in which operation was performed indicates that surgical intervention is not futile.

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## THE ANTITRYPTIC CONTENT OF THE BLOOD SERUM IN MALIGNANT DISEASE \*

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After Fermi and Pernossi, Camus and Gley, Pugliese and Coggi, and Hahn had drawn attention to the antitryptic action of normal blood serum, it was demonstrated by various observers that, under pathologic conditions, this may be either increased or diminished. Ascoli and Bezzola, more especially, were able to show that there is a marked increase in the antitryptic content of the blood serum in pneumonia up to the time of the crisis, while after the crisis, with the disappearance of the local symptoms, there is coincidently a marked decrease in the antitrypsin. Somewhat later Kolaczek, Bittorf, Wiens and others studied the antitryptic content of the serum in various diseases, finding a decrease in some and an increase in others. A systematic study of the question was, however, not made until quite recently, when Brieger and Trebing<sup>1</sup> drew attention more particularly to the marked increase of the antitryptic content of the serum in malignant disease.

The method which these investigators employed was essentially a modification of that of Müller and Jochmann. To this end, plates of Loeffler's blood serum are treated with tiny droplets of the serum to be examined, variously diluted with a 1 per cent. solution of trypsin. These plates are kept for twenty-one hours at 55 C. and then examined. The antitryptic action of normal sera is such that digestion of the plates at the point of contact of the droplet will occur with dilutions extending to 1:4, exceptionally to 1:6. In their first series of 35 cancer cases in which the diagnosis could be definitely made from the symptoms the dilution values were more than 1:6 in all but 4 cases; similar results were found in 8 cases of suspected cancer. Negative reactions were found in only 4 cases of definitely recognized malignant disease. In 6 non-malignant tumors there was no increase. Of non-malignant cases 36 were examined; of these, 5 showed an increase, namely, a case of extensive psoriasis (1:7) in a diabetic, another case, also in a diabetic, in whom there was a suspicion of cancer of the pancreas (1:9), one case of pernicious anemia, one of amebic dysentery and one of general septi-

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\*From the clinical laboratory of Dr. Charles E. Simon.

1. Brieger (L.) and Trebing: Berl. klin. Wchenschr., 1908, xlv, 1041, 1349, 2260.

cemia resulting from a gangrenous angina. Normal results only were obtained in cases presenting various types of gastric disturbance outside of cancer. Very curiously low values were seen in untreated syphilitic cases.

In a second paper, by the same writers, 55 further cases of cancer are recorded; in all values beyond 1:6 were found; in many, indeed, no digestion was observed even at 1:10. This list includes one case of sarcoma. In two non-cancerous tumors, normal values were obtained. In order to establish the influence of cachexia on the reaction *per se*, a number of cases in which no cancer existed were likewise examined. In these high values were also observed. This list includes cases of advanced tuberculosis, pernicious anemia, severe arteriosclerosis, chronic nephritis, tabes dorsalis and others. Brieger and Trebing accordingly regard their reaction essentially as an indicator of cachexia; but, as carcinomatosis and possibly also sarcomatosis may lead to cachexia relatively early without marked physical manifestations in the beginning, they are, nevertheless, inclined to view the reaction as important from the standpoint of differential diagnosis.

The third paper dealing with the same subject comes from von Bergmann and Meyer.<sup>2</sup> These investigators came to practically the same conclusions as Brieger and Trebing. Although using a different method they find a positive reaction in 92.7 per cent. of their cancer cases, as contrasted with 91.6 per cent. on the part of Brieger and Trebing. Of the non-cancerous cases in which a positive reaction was obtained, there may be mentioned isolated cases of hyperthyroidism (Basedow's disease), lues, myxedema, cholelithiasis, severe nephritis, severe pernicious anemia, tabes dorsalis, sepsis and dysentery. It is noteworthy, however, that a positive reaction in non-cancerous cases is exceptional. The reaction is manifestly not specific of cancer nor does it appear dependent on cachexia *per se*. Brieger and Trebing properly remark that, with critical application, it is a valuable factor in the clinical diagnosis of cancer. A normal antitryptic content, *ceteris paribus*, may well be viewed as pointing in a different direction.

During the past three months 67 cases have been examined in this direction in Dr. Simon's laboratory. The results are shown in the accompanying lists.

The technic employed was the same as that used by von Bergmann and Meyer, and is essentially that suggested by Fuld. To this end, constant quantities of a casein solution are treated with varying amounts of trypsin solution and constant quantities of blood serum. After

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2. Von Bergmann and Meyer (K.): Berl. klin. Wehnschr., 1908, xlv, 1673.

incubation at 37 C. for 30 minutes, the different specimens are acidified and the concentration of the trypsin noted in those tubes in which complete digestion of the casein has been prevented by the serum. The casein solution is prepared by dissolving 1 gram of casein in 100 c.c. of decinormal sodium hydroxid solution, neutralizing with decinormal hydrochloric acid against litmus and diluting with 0.85 per cent. saline solution to 500 c.c. For our trypsin solution we used a preparation of Fairchild's, which was quite satisfactory. Of the powder 0.5 gram is dissolved in 50 c.c. of 0.85 per cent. saline with the addition of 0.5 c.c. of normal sodium carbonate solution, the resultant solution being diluted tenfold (1:10) with 0.85 per cent. saline. The acetic acid mixture is composed of 5 c.c. of glacial acetic acid, 45 c.c. of alcohol and 50 c.c. of water.

In the beginning we attempted the preservation of the casein and trypsin solution by means of chloroform and toluol. This, however, was abandoned, as the results became inconstant and not comparable with those reached with fresh solutions. Both were accordingly freshly prepared whenever needed. The blood serum was always diluted to 1 in 50 and usually examined within a few hours after taking the specimens. The individual tubes each received 2 c.c. of the casein solution, 0.5 c.c. of diluted serum and varying amounts of the trypsin solution.

Preliminary experiments had shown us that, with normal sera, the minimal completely digesting dose of trypsin lay at 0.08 or 0.09. At 0.09 and 0.1 normal sera only gave a slight turbidity on subsequently acidifying with two drops of the acetic acid solution. For each case tubes were hence prepared in which the trypsin content varied between 0.09 and 0.8, the volume of trypsin being always brought to 1 c.c. with saline. For the 0.09 tube we commonly used 0.9 c.c. of a 1:10 dilution of the standard solution. In our experience an inhibitory effect on the part of the various blood sera beyond the normal showed itself in one of two ways: either by a mere intensification of the turbidity within the normal limits, or by a direct extension into the tubes containing larger amounts of trypsin. It is accordingly impossible to furnish numerical results, as in Brieger's method. In many other respects, however, that of Fuld is much more convenient and much more likely to be employed by physicians at large.

The arrangement of an individual experiment is seen in the following two examples, which represent actual cases. The first shows results in a normal person, the second in a patient with cancer of the stomach:

## TWO EXPERIMENTS, ONE ON NORMAL PERSON, ONE ON PATIENT WITH GASTRIC CANCER

Amt. of Casein Solution.	Amt. of Trypsin Solution.	Amt. of Saline.	Amt. of Serum (1:50).	Incubation for 30 min.; then acidity.	Result.
I. NORMAL CASE.					
2.0 c.c.	.09 c.c.	1.1 c.c.	.5 c.c.		Faint turbidity.
2.0 c.c.	.1 c.c.	.9 c.c.	.5 c.c.		Clear.
2.0 c.c.	.2 c.c.	.8 c.c.	.5 c.c.		Clear.
2.0 c.c.	.3 c.c.	.7 c.c.	.5 c.c.		Clear.
2.0 c.c.	.4 c.c.	.6 c.c.	.5 c.c.		Clear.
II. CANCER CASE.					
2.0 c.c.	.09 c.c.	1.1 c.c.	.5 c.c.		Flocculent precipitate.
2.0 c.c.	.1 c.c.	.9 c.c.	.5 c.c.		Flocculent precipitate.
2.0 c.c.	.2 c.c.	.8 c.c.	.5 c.c.		Marked turbidity.
2.0 c.c.	.3 c.c.	.7 c.c.	.5 c.c.		Marked turbidity.
2.0 c.c.	.4 c.c.	.6 c.c.	.5 c.c.		Clear.

Our results are collected in the two following lists:

## I.—SERIES OF CASES SHOWING AN INCREASED ANTITRYPTIC ACTION

- Mr. D.: Cancer of the pancreas.
- Mrs. X.: Hysteria (non-cachectic).
- Mrs. O.: Cancer of the breast (postoperative).
- Mrs. S.: Cancer of the breast (postoperative).
- Mrs. P.: Epithelioma of lower jaw (postoperative).
- Mrs. S.: Metastatic cancer of left inguinal glands (postoperative).
- Mrs. C.: Cancer of rectum.
- Mr. A.: Typhoid fever.
- Mr. E.: Epithelioma.
- Mr. R.: Cancer of testicle.
- Mrs. F.: Undiagnosed; operated on for symptoms of intestinal obstruction; tiny areas of fat necrosis everywhere; pancreas not enlarged, large mass about head of pancreas seemingly composed of fat with necrotic areas. Past history of syphilis. Recovery. Positive Wassermann reaction.
- Mr. P.: Amputation of foot. No diagnosis. Non-malignant.
- Mr. J.: Typhoid fever.
- Mr. G.: Carcinoma of cecum.
- W.: Probably malignant; mass in left iliac fossa, hemorrhages from bowel; loss of 50 pounds in weight.
- Mr. L.: Cancer of stomach.
- Mrs. S.: Not diagnosed; suspicion of cancer of stomach; exploratory incision with negative result.
- Mrs. S.: Cancer of uterus, advanced (inoperable).
- Mr. G.: Ulcer of stomach.
- Mrs. N.: Vomiting of pregnancy.
- Mrs. S.: Cancer of stomach.
- Mr. T.: Pernicious anemia.
- Mr. T.: Cancer of prostate.
- S. K.: Cancer of uterus.
- Mrs. S.: Melanotic sarcoma.
- Mr. S.: Cancer of stomach.

## II.—SERIES OF CASES SHOWING NO INCREASE OF ANTITRYPTIC ACTION

- Miss G.: Normal.
- Dr. S.: Normal.
- Dr. H.: Normal.
- Dr. L.: Normal.
- Dr. T.: Normal.
- Dr. T.: Normal.
- Miss M.: Normal.
- Miss R.: Normal.
- Mr. S.: Septic infection.
- E. H.: Gonorrhea and syphilis.
- Mrs. S.: Normal.
- Mr. V.: Normal.
- Mrs. M.: Uterine polypus.
- Mr. P.: Lipoma.
- Mr. F.: Psychasthenia.
- Mrs. G.: Normal.
- Miss C.: Normal.
- Mr. K.: Normal.

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| 19. Miss B.: Normal.                                 | 31. Miss K.: Probably malignant.       |
| 20. Miss S.: Normal.                                 | 32. J. K.: Gonorrhea.                  |
| 21. Miss N.: Normal.                                 | 33. Mr. F.: Fracture.                  |
| 22. Miss A.: Normal.                                 | 34. Miss E.: Multiple neuritis.        |
| 23. Dr. X.: Lipoma.                                  | 35. Miss O.: Adenocarcinoma of breast. |
| 24. Mrs. F.: (Non-malignant) Intestinal obstruction. | 36. Miss P.: Cholelithiasis.           |
| 25. Mr. X.: Cancer of rectum.                        | 37. Dr. N.: Normal.                    |
| 26. Mr. X.: Typhoid fever.                           | 38. Mr. P.: Normal.                    |
| 27. X.: Gonorrhea.                                   | 39. X.: Cholelithiasis.                |
| 28. Mr. S.: Dermoid cyst.                            | 40. Dr. J.: Normal.                    |
| 29. Mr. S.: Cancer of stomach.                       | 41. Ulcer of stomach.                  |
| 30. Mr. S.: Probably malignant.                      |  |

## SUMMARY OF RESULTS IN BOTH SERIES OF CASES

In forty-five non-malignant cases, 36, or 80 per cent., had normal antitryptic content, 9, or 20 per cent., had increased antitryptic content.

In twenty-two malignant cases, 5, or 22.7 per cent., had normal antitryptic content; 17, or 77.3 per cent., had increased antitryptic content.

An analysis of the cancer cases—and this is the point of most interest—shows an increased antitryptic content in 77.3 per cent. of cases and normal values in the rest. I would also emphasize the greater importance of a negative reaction in excluding the diagnosis of malignant disease, although markedly positive reactions may at times be regarded as an important positive symptom.

In one case in which a marked inhibitory effect was noted, and in which lactic acid reactions in the stomach contents alternated with normal conditions, and in which slight complement fixation was noted, an exploratory incision was advocated, but revealed nothing abnormal in the stomach. It is, of course, possible in this case that early malignant disease may exist in some other part of the body, but this will have to remain undecided for the present.

As regards the meaning of the reaction, it is scarcely possible to express more than a mere surmise, but it would not appear unreasonable to regard it as an expression of an antibody formation directed against tryptic ferments liberated during increased cell destruction in the body.

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# METHOD FOR ESTIMATING THE BLOOD FLOW IN THE ARM

## PRELIMINARY REPORT

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Of the various factors entering into the problem of circulatory dynamics the most important is the rate of blood flow. This can be determined experimentally by Ludwig's *Stromuhr* or some of its various modifications. More recently T. G. Brodie<sup>1</sup> has estimated the blood flow in an organ by suddenly occluding its efferent vein and measuring the change of volume by an oncometer. Under these circumstances the arterial blood enters the organ with undiminished speed at first, but soon the flow is retarded by the rise of pressure in the veins and capillaries. The organ therefore swells rapidly at first and progressively more slowly. The earliest portion of this curve represents the rate at which the blood enters under normal conditions. Brodie has shown that this method gives as reliable results as the *Stromuhr*. It is applicable only to organs from which all efferent blood can be collected by a single vein.

We have used Brodie's principle in order to determine the rate of flow in the arm of man. A distensible cuff similar to that used for determining arterial pressure was placed about the upper arm and an attempt was made so to adjust the pressure in the cuff that the veins should be occluded and the arteries left open. The resultant changes in the volume of the arm were recorded by a plethysmograph and a Brodie volume recorder. Certain precautions are necessary in order to obtain uniform results. In the first place, the pressure cuff must be inflated very rapidly. This is accomplished by connecting it with a large bottle in which the pressure has previously been raised slightly above that desired for the cuff. When the stop-cock between the two is opened the pressure is applied to the arm almost instantaneously. In the second place, the inflation causes a damming back of fluids which lie in the tissues beneath the cuff. The wider the cuff and the nearer to the plethysmograph the larger is the amount of fluid forced back into the latter. For this reason we have used a narrow cuff, about 3 cm. wide,

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1. Brodie (T. G.): The determination of the rate of blood flow through an organ. Reported at the Seventh International Physiological Congress, August, 1907.

and have placed it about 3 cm. from the opening into the plethysmograph. Under such conditions the increase of volume caused by the tightening of the cuff rarely exceeded 2 or 3 c.c. and was often less than this.

Another important question remains: Is it possible to occlude the outflow through the veins without affecting the arterial inflow? Theoretically this should be possible if the pressure applied to the tissues were in excess of the venous pressure and at the same time less than the diastolic arterial pressure. Under such conditions one should realize a parallel to Brodie's experiment. At first the blood would flow uninterruptedly into the arm, but after a time the distention of the veins, capillaries and surrounding tissues would impede the entrance of blood and the inflow would gradually lessen. We have recorded the volume changes after applying a series of gradually increasing pressure to the upper arm by means of the pressure cuff. Pressures below 30 or 40 mm. of mercury were usually insufficient to obstruct the veins even for short lengths of time, and the volume curve failed to rise uniformly after a few cubic centimeters of blood had entered. At somewhat higher pressures—usually from 40 to 80 mm. of mercury—all the volume curves from the arm were practically uniform. At still higher pressures the arteries were obstructed and the rate of inflow lessened until finally, at pressures above the arterial systolic pressure, the arteries were completely occluded and the only rise in the volume curve was due to the forcing of liquid back from beneath the pressure cuff. We believe that during the uniform series of curves obtained at various pressures (usually between 40 and 80 mm.) the veins were completely obstructed and the arteries open.

These curves show a gradually lessening rate of entrance of blood into the arm owing to the gradual increase of pressure in the veins, capillaries and surrounding tissues. The first portions of these curves show a nearly uniform rate of inflow, and usually about 10 c.c. of blood entered the plethysmograph without marked retardation (more than 20 per cent.). Sometimes only about 5 c.c. entered at a practically uniform rate, while again as much as 15 or 20 c.c. entered before retardation became marked. Up to the point when this occurs the swelling of the arm may be taken to represent approximately the normal rate of blood flow into the arm.

By this method the rate of flow was found to vary considerably in different individuals and to vary to a less extent in the same individual under different circumstances. The usual rate was from 3 to 5 c.c. per 100 grams of arm substance per minute, with extreme variations of



1.5 to 12 c.c. This agrees fairly well with the results obtained by Tschuewsky,<sup>2</sup> who used the *Stromuhr* on the legs of dogs and obtained inflows averaging 3.25 c.c. and varying from 1.93 to 4.77 under normal conditions, but increasing to as much as 11.8 after cutting the nerves and 6.89 after a brief obstruction of the artery.

At present we are measuring the rate in arms of patients with various pathologic conditions, but as yet have found no constant relation between certain diseases and the rate of flow. So far as we know, the only similar methods recorded for estimating the rate of flow in the arm are that suggested by O. Müller<sup>3</sup> and that of A. Müller.<sup>4</sup> Both these authors, however, stopped the circulation in the arm before measuring the rate at which the blood entered the plethysmograph. Consequently normal conditions were not approximated.

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2. Tschuewsky (J. A.): Ueber Druck, Geschwindigkeit, und Widerstand in der Strombahn der Arteria carotis und cruralis sowie in der Schilddrüse und im Musculus gracilis des Hundes. Arch. f. d. ges. Physiol., 1903, xevii, 210.

3. Müller (O.): Das absolute Plethysmogramm. München med. Wehnschr., September, 1908, lv, 1819.

4. Müller (A.): Methods zur Bestimmung von Schlagvolumen und Herzarbeit und deren Ergebnisse. Bed. ü. d. Verhandl. d. Kong. f. inn. Med., 1908, xxv, 325.

# PRIMARY PULMONARY ARTERIOSCLEROSIS WITH HYPERTROPHY OF THE RIGHT VENTRICLE

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The existence of sclerosis of the pulmonary arteries and its secondary effects on the right heart have long been recognized. These changes may depend on the circulatory disturbances in the lungs, due to extensive adhesive pleurisy, emphysema, fibroid changes in the lungs, but, above all, to chronic passive congestion of the lungs induced by left-sided heart lesion, especially mitral stenosis.

That there exists, however, a primary sclerosis of the pulmonary arteries with associated right heart hypertrophy has not been generally recognized. So far as I am aware, no case has been published in the English literature, and only a few cases have been reported abroad.

This fact seems to justify the publication of a case which came under my observation while I was engaged in study at the Pathologic Institute in Munich during the summer of 1908. I shall also take occasion to review briefly the cases which have previously been reported.

Unfortunately the clinical history of the case I am about to report is wholly unknown to me, and I can only epitomize briefly the pathologic findings.

The autopsy was conducted by Professor Dürck, Pathologic Institute, Munich, in July, 1908.

## SANDERS' CASE: PATHOLOGIC REPORT

The body was that of a well-nourished male, 33 years of age, who came to autopsy with the clinical diagnosis of heart disease. There were no pronounced evidences of edema of the body or extremities. On opening the thorax the lungs were found in a partially collapsed condition. The pericardium showed no evidence of disease and the pleuræ were free from adhesions. The heart showed an enormous hypertrophy and dilatation of the right ventricle. The apex of the heart was formed by the right ventricle and the left ventricle appeared as a sort of appendix of the right; its walls showed neither hypertrophy nor dilatation. The valves of the left heart were normal, but the tricuspid ring was dilated. The coronary arteries were normal, as well as all of the valves of the heart.

The pleura of the lungs was smooth and glistening and showed no adhesions. On section the lungs were moderately rich in blood and showed in the lower lobes hypostatic congestion. The lungs were free from fibrous induration and showed no old scars indicative of tuberculousis.

The cut surface showed the smaller branches of the pulmonary arteries to be considerably thicker and stiffer than normal, appearing to the naked eye as whitish, slightly projecting, prominences on the cut surface.

The secondary and tertiary branches of the pulmonary artery showed no local plate-like thickenings of the intima, but the wall appeared slightly more stiffened and thicker than normal. The origin of the pulmonary, as well as the aortic, arch showed on the intima a very few very slightly elevated yellowish butter-colored patches about as large as a rice-grain. Otherwise they were smooth and macroscopically normal.

The liver was slightly enlarged, showing, as did the spleen and kidneys, the condition of chronic passive congestion. There was otherwise no evidence of disease in any of the organs and no suggestion of syphilis.

The systemic blood vessels were free from macroscopic evidence of sclerosis.

Specimens of the origin of the aorta, pulmonary, the medium-sized and small branches of the pulmonary were studied microscopically. The vessels were cut with the freezing microtome and stained with Sudan III and hematoxylin, and also with carmine and Weigert's elastic stain.

The sections of the aorta showed in one place slight thickening of the intima, i. e., a hyperplasia of the connective-tissue cells. A number of these cells, chiefly those in the deeper layer of the intima, showed fatty degeneration of their cytoplasm. In most of these the nuclei were preserved and stained fairly well. The elastic fibers in these degenerated areas were preserved, but were hardly so distinct and refractory in outline as elsewhere. The thickened intima was made up chiefly of variously formed fibroblasts, spindle, pyramidal, etc. There was, however, a moderate round-cell infiltration. These changes were confined to the slightly thickened portion of the intima. The remaining portions of the intima, as well as the media and adventitia, showed nothing abnormal.

Sections from the pulmonary artery just above the semilunar valves showed slight general thickening of the intima, which was quite pronounced in some places. This thickening was generally of a hyperplastic character.

There were very few round cells, the predominating type being variously formed fibroblasts. The elastica interna was well preserved throughout; only adjacent to the pronounced local hyperplastic thickenings did it show lamellation. The interstices of these lamellæ were filled with the same hyperplastic connective tissue elements which predominated in the intima thickening. There was no fine fibrillation of the elastic fibers and the Sudan stain showed no fatty changes anywhere in the intima. The media and adventitia were normal.

Passing to the study of pulmonary branches of four or five millimeters diameter, microscopic sections showed the intima to be proportionately much more thickened, in fact, thicker than the media. This thickening involved both the superficial (i. e., axial or luminal) and deeper portions of the intima. In the former it was of the hyperplastic connective-tissue type, while the deeper portions showed, in addition, a marked increase of the elastic elements, being chiefly fine fibrillæ. There was no degenerative change demonstrable by the Sudan hematoxylin method.

The smaller pulmonary branches showed a similar condition; a pronounced thickening of the intima, generally, being thicker than the entire remaining portions of the vessel wall. The thickening was chiefly connective tissue hyperplasia, although considerable increase of elastic elements were present. No degenerative changes were observed.

In none of these sections did the vasa vasorum show any changes; a point which, it appears to me, is worthy of notice, since they spring from the bronchial arteries and belong to the systemic rather than the pulmonary circulation.

Reviewing briefly the chief points of interest in the case, we find a practically negative condition of the systemic circulatory organs, including the left heart and systemic blood vessels.

There is absolutely nothing in the lungs *per se*, such as sclerosis at the hilum, emphysema, fibroid induration, pleuritic adhesions, tuberculosis, or tumor growth, which could in any way account for the condition. Aside from conditions which were manifestly dependent on the failure of the right heart (passive congestion), the remaining organs of the body showed no pathologic alterations.

The arteriosclerosis of the pulmonary vessels involved chiefly the smaller and middle-sized branches, and sections from the trunk of the pulmonary showed only minimal intimal thickening. The right heart hypertrophy and dilatation was evidently of a secondary nature, depending on the primary condition in the pulmonary vessels. In support of this opinion we have a parallel in hypertrophy of the left ventricle from arteriosclerosis, and, furthermore, it is just those scleroses of the smaller branches, such as the renals, mesenteric and cerebral, which produce the most pronounced left ventricular hypertrophy.

#### KLOB'S CASE

The first similar case which I have been able to find in the literature was recorded by Klob,<sup>1</sup> who gives the autopsy report of a man, aged 59, who presented almost identical conditions with those reported in my case. The clinical history was unknown. The heart showed very marked hypertrophy and dilatation of right ventricle and auricle, the left heart was normal, and the valves showed nothing pathologic. The lungs were normal with exception of slight pleuritic adhesion at one apex.

#### CRUDELI'S CASE

Corrado Tommasi Crudeli<sup>2</sup> reported a case of a man, aged 42, who had often had rheumatism and bronchitis, and who died after a year's suffering from dyspnea and palpitation of the heart. The autopsy showed a small aneurism of the trunk of the pulmonary artery which he considered had originated from a marked endarteritic stenosis of the origin of both primary branches of the pulmonary.

#### WOLFRAM'S CASE

A. Wolfram<sup>3</sup> saw at autopsy a pronounced hypertrophy of the right heart with aneurismic dilatation of the pulmonary trunk and atheromatous changes in the pulmonary vessels extending to the finest branches.

None of these cases was studied microscopically.

#### ROMBERG'S CASE

Romberg<sup>4</sup> has given a quite complete clinical and pathological report of a similar case:

*History.*—A man, aged 24, who had muscular rheumatism one and a half years before the period of observation, but never had articular rheumatism or syphilis, was a moderate liver. About fifteen months before began to complain

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1. Klob: Wiener Wochenblatt, 1865, xxi, 45; cited by Romberg, see Note 4.
  2. Crudeli (C. T.): Schmidt's Jahr., 1870, cxlvii, 169.
  3. Wolfram (A.): Virchow-Hirsch Jahrb., 1883, ii, 147.
  4. Romberg (E.): Deutsch. Arch. f. klin. Med., 1891, xlviii, 197.

of shortness of breath, epigastric pressure, which increased, and headache and dizziness developed. The patient had been able to do light work until a few weeks before coming under observation. Physical exertion produced a marked cyanosis of the face. He had not complained of palpitation or edema of the feet. He was admitted to the clinic a week later, when a "peculiar heart affection, with swelling of the liver and spleen, was diagnosed" and digitalis and rest in bed were prescribed.

*Examination.*—The physical examination at this time showed a poorly nourished man, 156.5 cm. tall, slightly icteric. He had moderate dyspnea, temperature 36.4 C., and respiration 24. There was pronounced cyanosis of the skin and visible mucous membranes. The cheeks, extensor surface of arms, hands, knees and dorsum of the feet were a dark blue to bluish-red color. There was no edema. The precordial area was prominent; systolic apex impulse in the fifth left interspace, 7.5 cm. from median line and 4 cm. medialwards from the mammary line. This pulsation area was distinctly visible in the intercostal spaces to the margin of the sternum and upward to the third rib. A weak systolic thrill was felt in the fifth left intercostal space at the mammary line. There was no epigastric pulsation. The relative cardiac dulness extended 7 cm. in the fifth right interspace and 15 cm. in the fifth left interspace from the mid-sternal line. Auscultation showed a soft systolic murmur marking the first sound at the apex; at the end of systole there was a short, snappy sound immediately followed by the second sound. The large veins of the neck were not distended, and neither they nor the arteries revealed any adventitious sound on auscultation. The pulse was 116, small, equal and regular, and the arteries soft and not very full. Lungs were normal except a slight increase at their margins. The liver was enlarged. Urine, concentrated, specific gravity 1018— $\frac{1}{4}$  vol. albumin, positive for bile and negative for blood. Microscopic: rich in urates and a moderate number of leucocytes.

*Course of Disease.*—By absolute rest in bed, the patient was relieved somewhat, but dyspnea and cyanosis remained the same; the urine amount increased to about 1000 c.c., specific gravity varied from 1014 to 1020 and albumin increased. The average daily temperature was about 36 C. Digitalis remained without effect and the patient died about three weeks later with increasing cyanosis, edema and heart weakness.

Professor Cursehman had established a diagnosis of congenital heart disease and the cyanosis was considered due to a mixing of arterial and venous blood.

*Autopsy.*—Postmortem examination showed extensive but quite delicate right-side pleuritic adhesion, lungs slightly pigmented and edematous, cyanotic induration of spleen, liver congested and fatty, follicular catarrh of large and small intestines. The heart was almost twice as large as normal, the hypertrophy involving almost exclusively the right ventricle and chiefly confined to the conus. The coronaries were normal and all the valves intact. The pulmonary arteries showed diffuent sclerotic patches of various sizes; some of the larger branches showed dilatation, while the thickening sclerosis was more marked in the smaller branches.

#### MÖNCKEBERG'S CASES

Mönckeberg<sup>5</sup> has described two cases:

CASE 1.—*History.*—A young woman, aged 33, became ill in January, 1906, with symptoms of nervousness and anemia. In February there was increased cardiac dulness to the right with a murmur at each of the ostia, most pronounced at the pulmonary. The pulse was small and very rapid. The patient's condition grew worse, with vomiting, sweating, edema, brownish livid hue of the

5. Mönckeberg: Deutsch. med. Wchnschr., 1907, xxxiii, 1277.

skin, and prominent eyeballs; von Graefe's sign was present, but only moderate. The thyroid was not swollen. On April 5 the patient was admitted to the clinic. Cardiac dulness; right, 3 cm.; left, 12 cm. A constant systolic and occasional diastolic murmur were heard at the apex. A tremor soon became noticeable. The amount of the urine was 300-500 c.c.; specific gravity about 1025. Blood pressure, 125; later, 117. A masked form of hyperthyroidism was diagnosed, but myocarditis was considered. Under symptoms of increasing heart weakness, the patient died April 22, 1906.

*Autopsy.*—The thyroid and adrenals were normal, the lungs showed no pleuritic adhesion. The pericardium contained 200 c.c. of fluid. The heart was distinctly enlarged, involving chiefly the right auricle and ventricle, while the left ventricle appeared as a sort of appendix to the right. There was a pronounced widening of both of the primary branches of the pulmonary. The trunk of the pulmonary, as well as its chief branches, showed slightly elevated yellowish white patches in the intima. The local thickening extended to the branches of the second and third orders, where the sclerosis became more diffuse and pronounced, as shown by microscopic examination. The lungs showed moderate pigmentation and edema, and on section were of a reddish-brown color. The intima of the aorta was smooth, the valves of the heart were all normal. The sclerosis was much more marked in the very small pulmonary branches, where the intima was four times as thick as the media. The intima thickenings were relatively poor in cells, but contained numerous fine elastic fibers. No retrogressive changes were found except in the larger branches. The pulmonary and the bronchial veins were not pathologic.

*CASE 2.—History.*—A man, aged 56, came under treatment in January, 1906, for dyspnea and palpitation. Examination gave the diagnosis of mitral insufficiency with failing compensation. The transverse area of dulness was markedly increased, there was a systolic murmur at the apex, swelling of the liver and edema of the feet. There were pressure symptoms in the stomach. A diagnosis of mitral insufficiency was made. Under the administration of caffeine and theobromin-sodium salicylate, with absolute rest, the general conditions improved for about four weeks. Notwithstanding good heart action and pulse, the liver swelling and edema remained the same. November 5 the patient entered the clinic, where there was recorded marked cyanosis, edema of the body, hands and feet, marked venous pulse. The liver was enlarged and pulsating. The heart dulness was 5 cm. to the right and 11.5 cm. to the left of the mid-sternal line. There was left-side hydrothorax. A loud systolic murmur was heard at the apex and a rather soft second sound. The patient died the same day he entered the clinic.

*Autopsy.*—Left lung: slightly adherent pleura at apex and posterior surface. Right lung: total, but delicate, pleural adhesions. Heart, in general, enlarged, both right ventricle and right auricle involved, the former markedly, the latter moderately dilated. Right ventricle wall stiff, 7 mm. thick. Left ventricle not dilated, wall normal thickness. The valves were all normal and the endocardium negative, except at the attachment of the anterior mitral segment and the attachment of the aortic valves, where there was slight thickening. The mitral ostium was patulous for two fingers and the tricuspid for four. Above the pulmonary sinus an adherent thrombus began, extending upward into the right pulmonary, completely occluding the branch to the lower lobe of the lung. The branches to the middle and upper lobe contained soft emboli, partially occluding these branches. These thrombi were lamellated and partially adherent to the vessel wall, partly dark red and partly gray or brownish color. The cut surface of the lungs was edematous and engorged with blood, the walls of the pulmonary branches thickened; many contained thrombi. The inferior vena cava contained a firmly adherent thrombus, extending into the iliac. The aorta showed a few

whitish elevations on the intima. The other organs of the body were cyanotic. The beginning of the trunk of the pulmonary showed wave-like yellowish elevations on the intima. Notwithstanding the vessel was dilated, its walls appeared thickened. Microscopically the intimal thickening consisted of connective tissue hyperplasia, rich in elastic fibers. There were no degenerative signs present. The thrombi showed in many places incipient organization, proving that they must have existed a considerable time before death. The intimal thickening involved more the medium-sized than the extremely small vessels. Indeed, some of the small branches showed dilatation without thickening of their walls, and some contained thrombi. The pulmonary veins and the bronchial arteries were not pathologic.

#### KITAMURA'S CASE

Kitamura<sup>6</sup> has very recently reported a case of a 33-year-old man who indulged in alcoholic excesses (thirty glasses of beer, besides wine and whisky, daily), who died with symptoms of heart weakness. He was very fat, weighing 245 pounds. The heart was markedly enlarged, with marked thickening of the wall of the left ventricle, but much more pronounced thickening of the right. The valves and endocardium were normal. The pulmonary artery and its branches showed pronounced thickening of the intima, which was of a proliferative character and much disposed to degeneration of a fatty and hyaline nature. The media showed only a disorganization of the elastica. The entire body was strikingly congested. "Kitamura considers the condition due to a plethora vera induced by excessive consumption of beer. This opinion finds some support in the work of Bollinger on the beer heart."

The consideration of these seven cases furnishes sufficient evidence, I think, to establish the existence of a primary pulmonary arteriosclerosis which must be taken into account as an etiologic factor in hypertrophy and dilatation of the right ventricle. The clinical features of the condition can not be said to be yet sufficiently developed to admit of a diagnosis, *intra vitam*, but the careful correlation of clinical symptoms with pathologic studies in a few more cases will, I believe, furnish a rather characteristic picture. The application of the x-ray and the cardiosphygmograph may throw some light on the condition. The fact that a high percentage of these cases have occurred in young individuals without the evidence of previous disease to account for the cardiac condition; further, that the course of the disease has been rather rapidly progressive, and that ordinary cardiotherapeutic measures have been quite ineffectual, should be taken into consideration. The etiology remains, for the present, wholly undetermined.

6. Kitamura: Zeitschr. f. klin. med., 1908, lxx, 14.

NOTE.—The following references may also be found of interest in this connection:

Lubarsch-Oestertag: Ergebnisse der Pathologie, 1907; lecture on arteriosclerosis by Thoral.

Zeigler's Lehrbuch der allgemeine Pathologie, ii.

Kaufmann (E.): Lehrbuch der Speciellen Pathologie.

Joras: Wesen und Entwicklung der Arteriosclerosis, Wiesbaden, 1903.

Aschoff: Ueber Arteriosclerosis und andere Sklerosen des Gefäßsystems. Med. Klin., 1908, No. 1.

# DEMONSTRATION OF THE TRICHINELLA SPIRALIS CIRCULATING BLOOD IN MAN

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AND

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Since the first description of trichiniasis in man by Owen, in 1825, opinion has been divided as to the channels by which the embryos travel from the intestine to the muscles. Leuckart's<sup>1</sup> authority has been prominent in maintaining the traditional view that trichinellæ migrate act through the connective-tissue planes, and this statement is frequent in text-books. The only experimental evidence for this has been the finding of the worm in the peritoneal, pleural and pericardial cavities, the well-known fact that the diaphragm, and especially its crura, usually contains more encysted parasites than the rest of the body musculature.

Against this view the weight of experimental proof has been accumulating gradually. Zenker,<sup>2</sup> in 1860, took the stand that the dissemination of the embryos to the muscles was probably by way of the chyle ducts and blood stream. Fiedler,<sup>3</sup> in 1864, found embryos in the right heart of experimentally infected rabbits. Cerfontaine<sup>4</sup> found the female worms in the Peyer's patches and mesenteric lymph nodes of rats. Askanazy clearly demonstrated the embryo in the abdominal lymph channels. Geisse<sup>5</sup> reported similar observations. Graham,<sup>7</sup> in 1897, in an admirable experimental study, considered that he had demonstrated dissemination by the blood stream through the finding of embryos in a section of a rat's artery, in the muscle capillaries, near hemorrhagic extravasation in the heart muscle, and in hemorrhagic lesions of the lung. He

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1. Leuckart (R.): Die menschlichen Parasiten, Leipzig, 1876, ii, 656.

2. Zenker: Virch. Arch. f. path. Anat., 1860, xviii, 561; also Arch. f. Med., 1870, viii, 387.

3. Fiedler: Beiträge z. Entwicklungsgeschichte der Trichinen, etc., Arch. Heil., 1864, v, 3.

4. Cerfontaine: Contribution à l'étude de la trichinose. Arch. de biol., xiii, 125; also Centralbl. f. Bakteriöl., xxi, 1897, 402.

5. Askanazy: Zur Lehre von der Trichinose. Centralbl. f. Bakteriöl., xv, 225; also Arch. f. path. Anat., Berl., 1895, xlii, 141.

6. Geisse: Zur Frage der Trichinenwanderung. Deutsch. Arch. f. klin. Med., 1895, lv, 150.

7. Graham: Beiträge zur Naturgeschichte d. Trichina Spiralis. Arch. mikr. Anat., 1897, I, 219.



believed that the rapidity of distribution throughout the body argued strongly for their transference by the blood stream. Frothingham,<sup>8</sup> in 1906, in summing up the evidence, states that, although the embryos probably are distributed by the blood, they are not described as being found free in the blood stream. He said: "It remains, therefore, to demonstrate the position of the trichina embryo in the lymph glands; to demonstrate them in the blood stream in man; to find any undescribed lesions, and to confirm those already described." His autopsy case revealed embryos in the sinuses of the mesenteric lymph nodes and in the liver sinusoids, proving the first point. The present observation is put on record because demonstrating the second link in the chain of evidence, for the first time in man, so far as a careful search of the literature reveals.

Staübli,<sup>9</sup> in 1905, reported to the German Congress on Internal Medicine the recovery of embryos from the heart blood of infected guinea-pigs in every instance. The method by which he achieved this remarkable result was by taking a small quantity of blood with 3 per cent. acetic acid, centrifugalizing, and examining the sediment. Last year he made the demonstration still more conclusive for artificially infected animals by finding the embryos in blood drawn from the guinea-pig's ear, at one time as late as twenty-seven days after infection.<sup>10</sup> The quantity of blood required was so small—only a fraction of a cubic centimeter—that he ventured the belief that his method of dilution with 3 per cent. acetic acid would be adequate for the detection of the trichinella in blood drawn from a simple finger puncture in man, and might become a ready means of diagnosis. Up to date, no reports of such findings have yet appeared in literature.

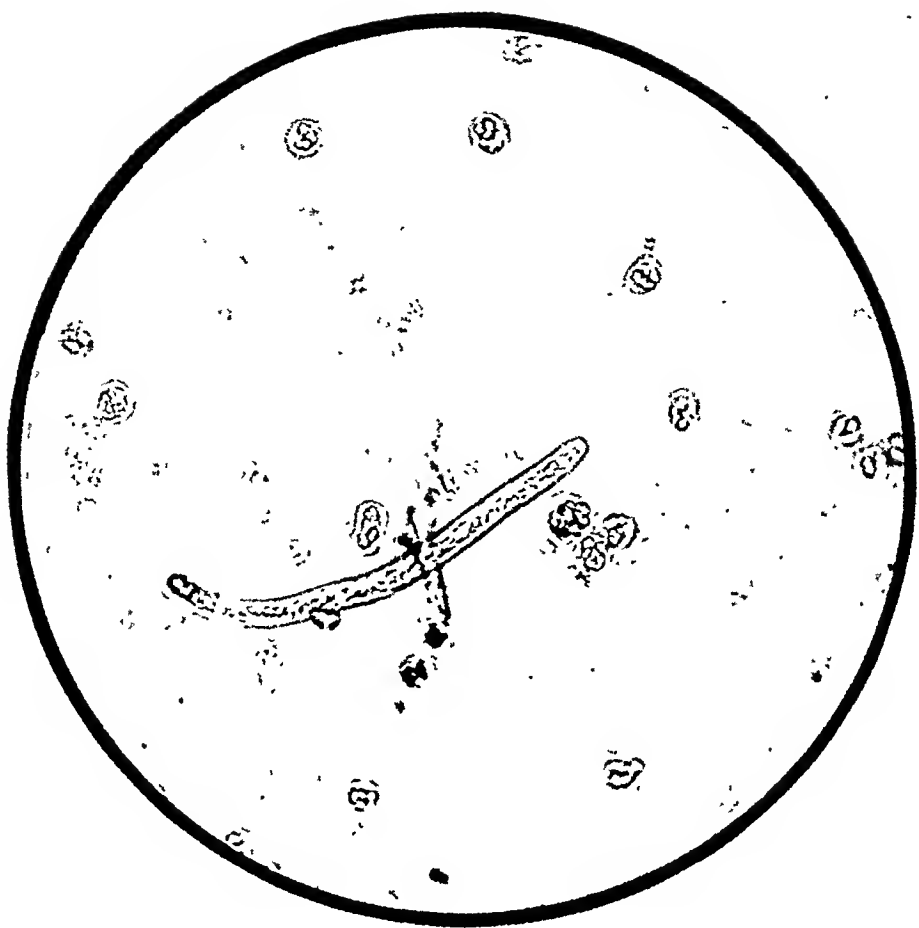
The case in which this positive finding was obtained was one of a family epidemic of trichiniasis occurring in the practice of Dr. Louis J. Lipset, to whose courtesy we owe the privilege of studying and reporting it. The family was seen first in consultation on March 17, and the probable diagnosis of trichiniasis made from the clinical symptoms, especially the occurrence of edema about the eyes and the finding of well-marked eosinophilia. The important facts in the clinical history of the cases are as follows:

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8. Frothingham: A contribution to the knowledge of the lesions caused by trichinella spiralis in man. Jour. Med. Research, 1906, x, 483.

9. Staübli: Klinische u. exper. Untersuchungen über Trichinosis. Verhandlung des Kongress f. klin. Med., Weisbaden, 1905, 354.

10. Staübli (C.): Beitrag zum Nachweis von Parasiten im Blut. Münch. med. Woch., 1908, lv, 2601.



Embryo of *Trichinella spiralis* in blood laked with 3 per cent. acetic acid. Leucocytes and disintegrated red cells also are shown ( $\times 800$ ).

ARCHIVES OF INTERNAL MEDICINE

ILLUSTRATING ARTICLE BY DR. WILLIAM WORTHINGTON HERRICK AND  
DR. THEODORE C. JANEWAY



*History.*—The family, Italians, consisted of father and mother, seven girls and one boy; the mother and all the girls had displayed symptoms of the disease, the children in very mild form, while the mother was seriously ill. The father and son had completely escaped. Inquiry showed that pork chops had been eaten for the mid-day meal, February 24, the father and son being then away from home. No other probable source of infection could be discovered, and the date of this bears the proper relation to the onset of symptoms. The Health Department is at present investigating this feature of the epidemic.

*Clinical Course.*—The chronology of the cases is as follows:  
 Case 1 (March 1).—Five days after the eating of the pork chops, the youngest child, aged two years, was taken with diarrhea of two days, followed by swelling of the eyelids and back of neck, fever for two days, followed the head was painful. Total duration of illness about seven days. March 21, eosinophiles, 7.5 per cent.

Case 2 (March 4).—Child of 11 years was taken with diarrhea of two days' duration, then chilliness, fever, headache and slight swelling of the eyelids. This child had no muscular pain and was not in bed. March 21, eosinophiles, 37 per cent.

Case 3 (March 9).—Child of 10 years came down with diarrhea of two days' considerable swelling of the eyelids, fever and moderate prostration, and was in bed four days. No muscular pains. March 21, eosinophiles, 28 per cent.

Cases 4 and 5 (March 9).—Two other children, twelve and seven years of age, were taken somewhat acutely ill with vomiting as well as diarrhea, and were in bed eight days. Both had marked swelling of the face and neck, and complained of pain on movement of the neck. March 21, eosinophiles, 7.5 per cent. in the eldest child and 24 per cent. in the other.

Case 6 (March 9).—The mother was also taken sick on this day. Onset sudden, with diarrhea, fever, and vomiting, followed in one day by swelling of the face and neck, with pain and stiffness of the neck on movement and tenderness to pressure. She became rapidly more ill and on March 18 was delirious, with much pain on movement, and tenderness of her muscles, occasional weakness of arms and legs, and indefinite signs of consolidation over her left upper lobe. The next day similar signs were heard over the right upper lobe. The reflexes were not lost. Her temperature reached 104 degrees and pulse for several days was 130 to 140. March 24, she was free from delirium, lung signs had disappeared and she was evidently mending. March 18, the eosinophiles were 8 per cent., polymuclear neutrophils 84 per cent. March 19, leucocyte count 11,000. Her urine showed a moderate amount of albumin, with some coarse granular casts, red cells and leucocytes, and a trace of bile.

Case 7 (March 12).—A child, of four, was taken sick with some vomiting and diarrhea, followed by fever, swelling of the eyelids and some pain and stiffness of the neck. In bed three days. March 19, eosinophiles, 29 per cent.

Case 8 (March 15).—Child of eight had slight gastrointestinal disturbance and fever, and developed a little edema of the eyelids, without muscular pain or tenderness anywhere. She was in bed one day only. March 18, eosinophiles, 19 per cent.

*Blood Examination (March 19).*—The blood was taken from the arm veins of patients 6, 7 and 8, and diluted with ten parts of 3 per cent. acetic acid according to Ståhl's directions. A large amount of blood—about 10 c.c.—was taken in the belief that the subsequent search for embryos would be facilitated thereby. In the blood from the mother (Case 6), four embryos were found in more than an hour's search. None were found in the blood of the two children. March 21st, 1.5 c.c. of blood were again taken from the arm vein of the mother and laked with about fifteen parts of the acid. Two trichinellæ were found easily,

without protracted search. The accompanying illustration is from a photomicrograph made in the fresh state a few hours later. Attempts to identify the parasites in dry smears of the sediment, stained with methylene blue and by Wright's method, were unsuccessful, although Staübli seems to have had no difficulty with this in his animals. The fresh specimens were examined by Dr. E. G. Janeway, Dr. Simon Flexner and Dr. Horst Oertel, and considered characteristic trichinella embryos. March 24, 3 c.c of blood were taken from Case 4, but no embryos could be found. The stools of the mother were examined twice, one of these times after the administration of half a gram of thymol, but no adult worms were discovered.

A careful survey of reported cases has failed to disclose a single one in which parasites had been detected in the feces of a living patient. Whether this would be possible during the earliest stage of the infection, when the diagnosis is never suspected, is questionable. It seems probable that after the diagnosis has been made from the symptoms attending muscular invasion, the adult worms are largely beneath the mucous membrane of the bowel, as well described in Frothingham's<sup>11</sup> recent paper in THE ARCHIVES. As a result of this study we feel justified in concluding that the final proof of the distribution of the *Trichinella spiralis* by way of the blood stream has been obtained in man, and in hoping that subsequent observation may prove the examination of the blood by Staübli's method a useful means of early diagnosis of the disease, where the clinical symptoms and the presence of eosinophilia have rendered its existence probable. There seems no question that the examination of the feces as a means of diagnosis is practically fruitless. The consent to the removal of a portion of muscle is not always had with ease; in our case it was entirely impossible to obtain it. The examination of a portion of excised muscle may give negative results, even when the disease exists, and less painful methods of diagnosis are certainly desirable.

We are indebted to Mr. A. J. Martin, artist of the Russell Sage Institute of Pathology, for the accompanying photomicrograph.

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11. Frothingham (C., Jr.): The intestinal lesions caused by *trichinella spiralis* in rats. THE ARCHIVES. INT. MED., 1909, ii, 505.

# MENINGOCOCCUS SEPTICEMIA WITH STERILE CEREBRO- SPINAL FLUID; IRIDOCYCLITIS; FLEXNER'S SERUM; RECOVERY \*

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The specific relation of the diplococcus of Weichselbaum to epidemic cerebrospinal meningitis is established beyond question. Investigations of the last few years have aimed to solve the mystery as to the sources of infection and the route taken by the invading organism in reaching its objective point in the meninges of the brain and cord. The first light on these questions came from the discovery of Albrecht and Ghon<sup>1</sup> that organisms morphologically identical with the *Diplococcus intracellularis* could be found in the nasal secretions of some of the patients. This observation was quickly followed by the proof that, while some of these organisms resembling the diplococcus of Weichselbaum belonged to other species, there was no doubt that the specific excitant of meningitis could be found in the nasal fossæ of some of the patients and also of others who have not had the disease but had come in touch with patients. Thus Flügge<sup>2</sup> found the meningococcus in the nasal secretions of patients 4 times in 44 trials, von Lingelsheim<sup>3</sup> 182 times in 787 examinations, while Koplik<sup>4</sup> quotes Goodwin and Sholly to the effect that the organism can be found in the nasal mucus in 50 per cent. of patients during the first two weeks of the disease and in 10 per cent. of those who come into contact with the patients. It seems therefore established that the respiratory tract, especially the nasal fossæ, is the usual avenue of entrance for the organism. The route by which the bacteria make their way from this outpost into the cranial cavity has thus far been the subject of speculation. The popular theory has been that the meningococcus makes its way directly through the sphenoidal or ethmoidal sinuses or the ethmoidal plate to the base of the brain. The facts, so far as they are at present known, lend support to that theory. Evidence is, however, accumulating that it is possible that a general meningococcus septicæmia may occur in the absence of a meningitis and that the systemic circula-

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\*From the Service of Dr. F. P. Kinnicutt in the Presbyterian Hospital.

1. Albrecht and Ghon: Wien. klin. Wochenschr., 1901, xiv, 984.

2. Flügge: Klin. Jahrb., 1906, xv, 353.

3. Von Lingelsheim: Klin. Jahrb., v, 373.

4. Koplik: Osler's Modern Medicine, ii, 499.

tion may, at least in some cases, be the pathway by which the organism reaches and lodges in the meninges.

That the meningococcus may be found in the blood in certain cases of epidemic cerebrospinal meningitis has been known for some time. In a recently published article Duval<sup>5</sup> reports such a finding and has collected from the literature a number of others. The first positive blood finding is credited to Gywn in one of Osler's patients. Warfield and Walker have reported 1 case, Lenhartz 2, Robinson 1 in 6 cases examined, Möller 1, Martin and Rhode 1, and Elser, in 41 cases of cerebrospinal meningitis, found the *specific coccus in the blood in 10*. On the other hand, Bettencourt and Francis<sup>6</sup> report 6 cases in which the blood examination during life was negative and 3 in which the organism was found in the heart blood, and Councilman, Mallory and Wright, in 35 cases, made cultures from the heart blood with negative results. Flüggé<sup>7</sup> and Rautenberg<sup>7</sup> each report failures to cultivate the meningococcus from the blood.

In addition to these reports collected by Duval, I have been able to find 2 positive findings made by Cochez and Lemaire,<sup>8</sup> 2 by Jacobitz,<sup>9</sup> 1 by Kutscher,<sup>10</sup> and 1 by Jäger.<sup>11</sup>

In a number of other cases the specific coccus has been found in locations indicating a systemic infection. Thus Fronz<sup>12</sup> found the organism in the meningeal exudate and in the right ankle, and Osler<sup>13</sup> some years ago reported a similar observation. Gradwohl,<sup>14</sup> in a postmortem examination of a pregnant woman who had died on the third day of her illness, found the meningococcus in the meninges of both the patient and the 7 months fetus, and also in pus from the mother's ear, although cultures from the lungs, blood, placenta and uterus were negative. Jäger<sup>11</sup> reports finding the organism in the urine in one case during life. A general distribution of the organism throughout the body is reported by only two observers. Jäger found it in the pericardium, pleural exudate, liver, spleen and pus in the pelvis of the kidney in 1 case, and Duval isolated it from the eye, pericardium, heart's blood, meninges and cerebrospinal fluid. Wintersteiner and Tooke (see Duval<sup>5</sup>) each recovered the organism from the spinal fluid and found it present in smears

5. Duval: Jour. Med. Research, 1908, xix, 258.

6. Bettencourt and Franca: Ztschr. f. Hyg., 1904, xlv, 463.

7. Rautenberg: Veröffentl. a. d. Geb. d. Mil.-San.-Wes., 1905, No. 31, 34.

8. Cochez and Lemaire: Baumgarten's Jahresbericht, 1902, xviii, 91.

9. Jacobitz: München. Med. Wehnschr., 1905, lii, 2178.

11. Jäger: Die Epidemische. Meningitis als Heereseuche, Berlin, 1901, pp. 196, 198.

12. Fronz: Wein. klin. Wehnschr., 1897, x, 351.

13. Osler: Boston Med. and Surg. Jour., 1898, cxxxix, 64.

14. Gradwohl: Philadelphia Med. Jour., 1899, iv, 445.

from the eyes, in which iridocyclitis was present, but could not obtain it in cultures from the latter site. Von Drigalska<sup>15</sup> cultivated the organism from herpetic vesicles on the ear, although he could not obtain it from the blood of the patient.

It thus appears that in a certain number of cases of cerebrospinal meningitis the meningococcus may be found not only in the spinal fluid, but in the blood or in various sites which indicate systemic infection. The number of such systemic infections thus far recorded is small, however, and we must regard them as rare. Duval, summing up his study, notes this fact and adds that there is at present no authentic case on record in which the meningococcus has produced lesions outside the meninges in the absence of a pre-existing meningitis.

In 1902, however, Salomon<sup>16</sup> reported the following case:

The patient, a laborer's wife, aged 32, was seized on July 30, 1901, with pains and swellings in her hands, elbows, and knees. On the following day she had a chill, followed by fever, and an eruption on the hands and feet, and became weak and faint. She was admitted to hospital on August 3. She was then suffering from a high fever, and the constitutional symptoms of a severe infection without focal signs, and had a profuse eruption resembling erythema exudativum. The fever and other symptoms persisted. On August 7 a blood culture yielded the meningococcus. From this time on there was no radical change in the patient's condition, the fever continuing, and new crops of the eruption appearing from time to time, until the end of September, when she developed signs of meningitis and lumbar puncture gave vent to a characteristic turbid fluid containing meningococci. The patient finally recovered in December. She had been sick for two months before the advent of the meningitis, and the meningococcus had been found in the blood nearly two months before the lumbar puncture, but as there is no record of a lumbar puncture having been made before the development of the symptoms of meningitis, the possibility of the presence of a meningitis early in her disease is not excluded in this case.

The following case, reported in October of this year by Liebermeister,<sup>17</sup> is free from that objection:

A laborer, aged 59, was admitted to hospital Feb. 25, 1908, complaining only of pain and stiffness in both shoulders. The beginning of his trouble he could not definitely place. The patient showed a high fever with signs of severe infection but no focal symptoms. There was a roseola resembling that of typhoid. On March 1 a blood culture yielded organisms later proved to be Weichselbaum's diplococcus. On March 7 lumbar puncture gave a clear fluid, under normal pressure, and containing no sediment. On March 18, 20 and 31 cultures from the blood still gave meningococci. On April 8 and 18 further cultures were negative. During all this time the fever of septic type continued, the eruption developed in repeated crops, and the patient had pains about various joints and some rigidity of the extremities. He had, however, no rigidity of the neck, no Kernig, no signs of involvement of the cranial nerves, so that there appears no good rea-

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15. Von Drigalski: *Deutsch. med. Wchnschr.*, 1905, xxxi, 982.

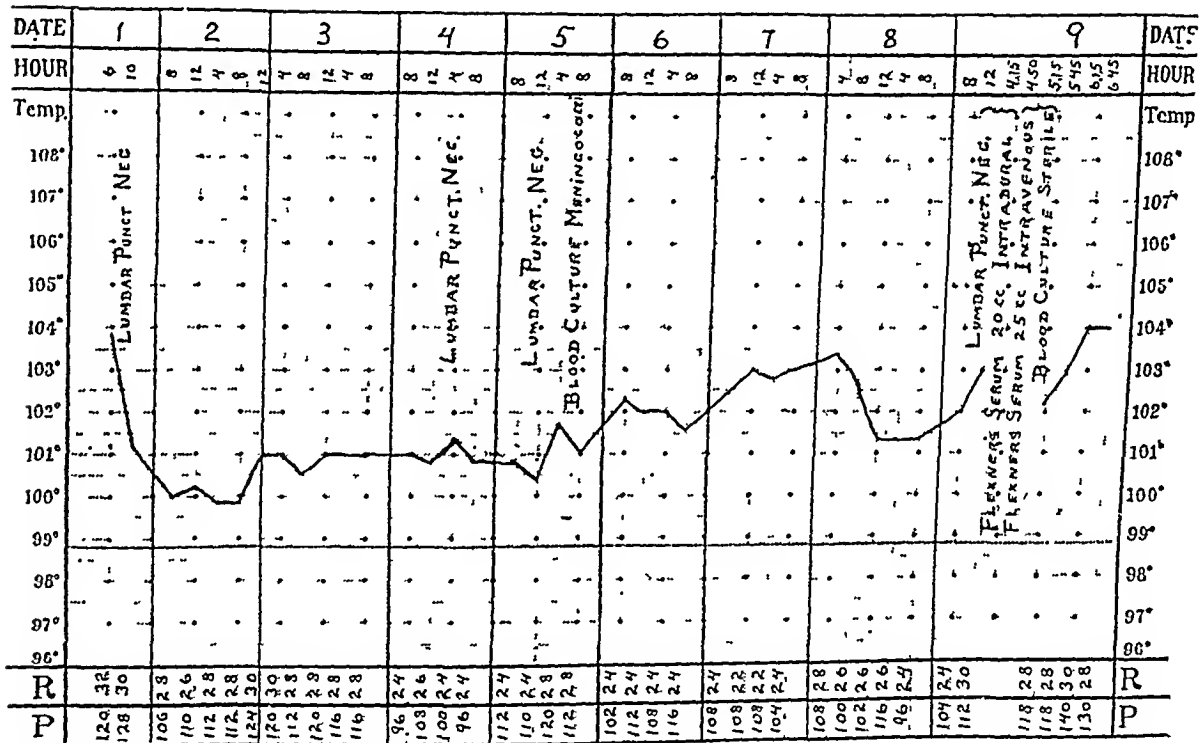
16. Salomon: *Berl. klin. Wchnschr.*, 1902, xxxix, 1045.

17. Liebermeister: *München med. Wchnschr.*, 1908, lv, 1978.



son for assuming that the patient had meningitis, especially in view of the negative results of the lumbar puncture (2). In May the patient developed an abscess on one arm, in which the common pyogenic organisms were found, but no meningococci. Finally the fever gradually subsided, the general condition improved and the patient recovered toward the end of June. In view of the evidence this case must, it seems, be accepted as a meningococcus septicemia without meningitis. As will later appear, I do not record this as proved by the negative results of the lumbar puncture alone; but the absence of the clinical signs of meningitis during the many weeks of observation and the normal spinal fluid constitute as strong evidence as can be had, so long as the patient recovers.

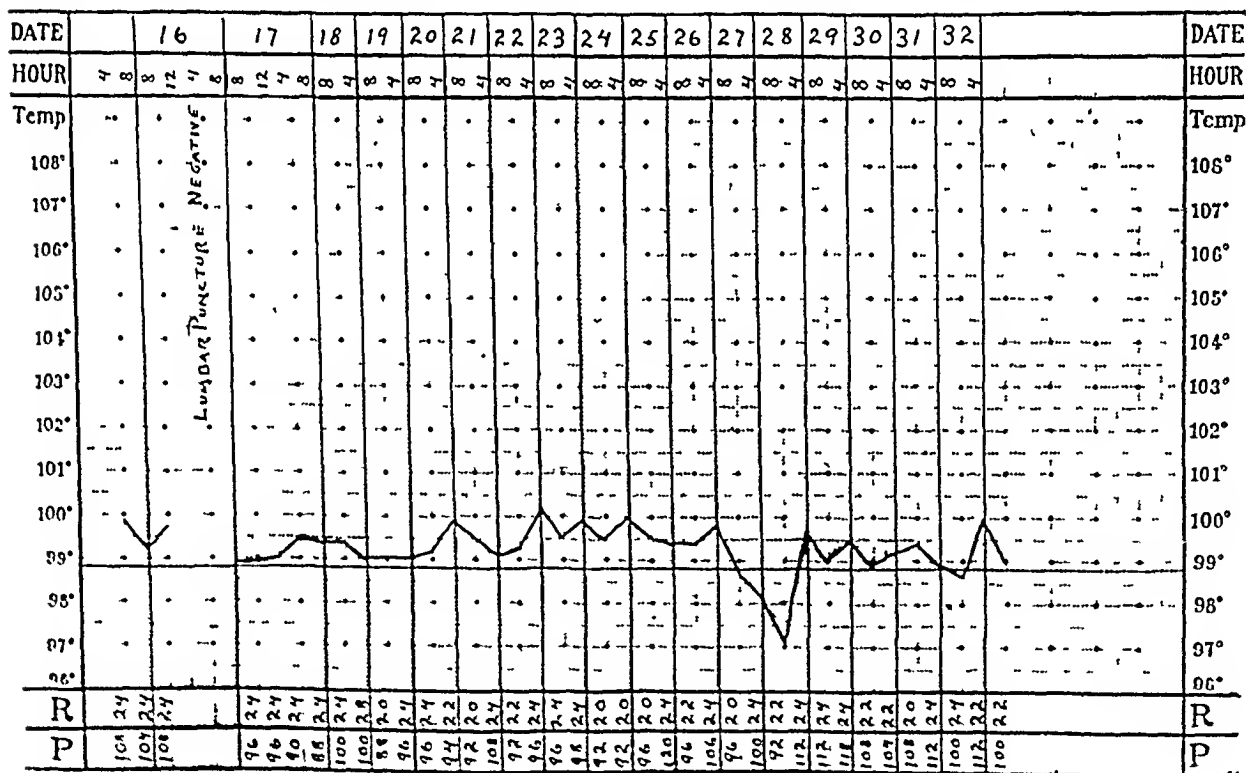
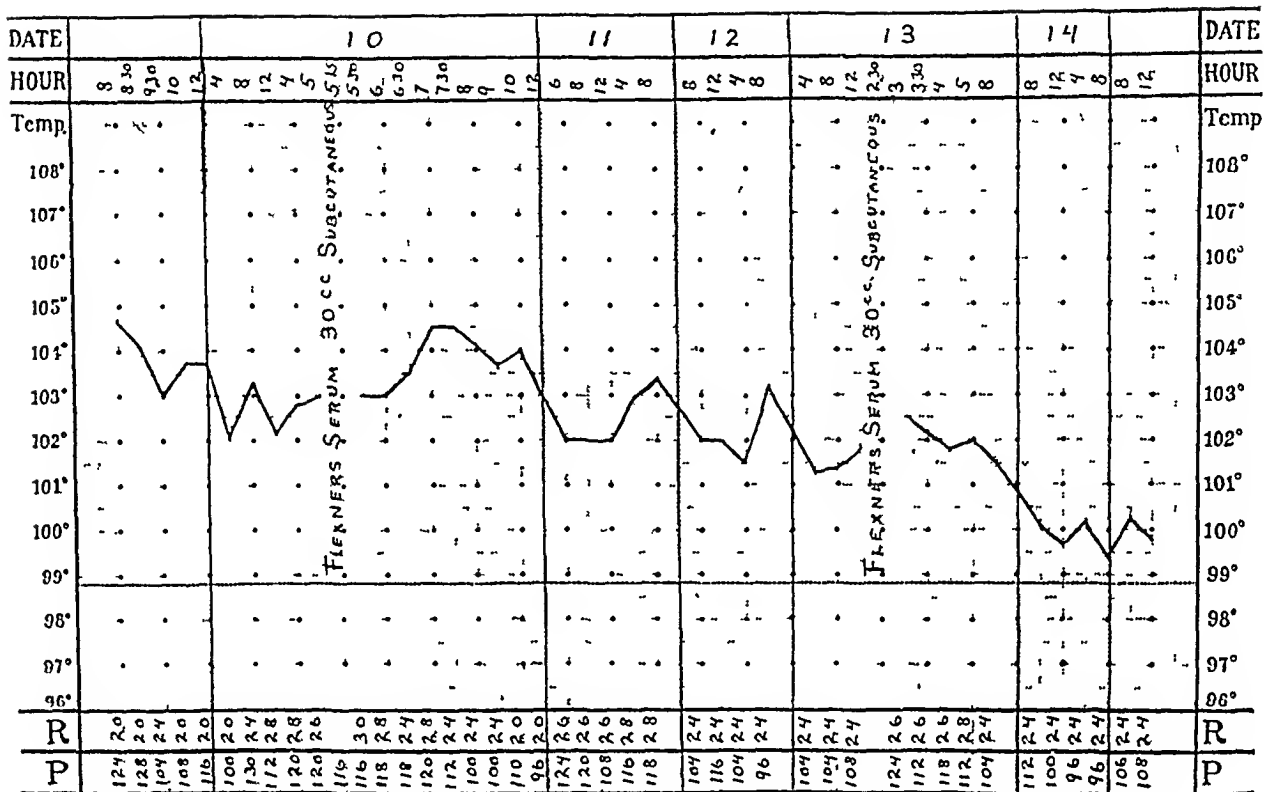
Andrewes,<sup>18</sup> pathologist of St. Bartholomew's, in 1906, reported the following decisive experience:



A physician, aged 52, was suddenly taken sick on the morning of Feb. 12, 1906. A few spots appeared on the face at noon. By evening a profuse hemorrhagic purpura had developed. The patient was moribund. Temperature was 99.4, pulse imperceptible, respirations 34; intracellular cocci found in the polynuclear leucocytes of the blood, proved by cultural studies and pathogenicity to be the *Diplococcus intracellularis*. Autopsy showed no meningitis either in the gross or microscopically. Extravasated meningeal blood, however, yielded a more abundant growth of the diplococci than did that of the heart.

Andrewes concluded that the case was proved to be one of blood infection by the meningococcus without meningitis.

18. Andrewes: Lancet, London, 1906, i, 1172.



Temperature Chart of a Case of Meningococcus Septicemia from October 5 to November 6.

In view of this evidence of the possibility of systemic infection by the meningococcus in the absence of meningitis, I wish to put on record the following case:

*Patient.*—S. P., aged 15, Russo-American, was admitted to the Presbyterian Hospital Oct. 5, 1908. Her family history was irrelevant. There was no contagious disease in the neighborhood; no meningitis among her friends.

*History.*—The patient was born in New York; lived under fair tenement-house conditions; had never menstruated. From birth up to the age of 2 she had frequent hemorrhages from the navel. Since then she enjoyed good health. She had had no previous illness except measles eight years ago, uncomplicated.

*Present Illness.*—On October 4 the patient was perfectly well. She went to a holiday dinner and was said to have greatly overeaten. About midnight she vomited three or four times. Vomitus consisted of green undigested food; vomiting was not projectile. The rest of the night the patient seemed to sleep quietly. On the morning of October 5 she complained of slight headache. The child did not seem very ill and the parents went to the synagogue, leaving her at home alone. At noon when they returned the child seemed as if dead, her face was yellow, and there were many dark spots on the body. She did not recognize her parents; the urine and feces were passed involuntarily. After that she was in a stupor; shook a little but had no real convulsions. She had no vomiting, and could swallow a little. The eyes were closed. She was brought to the hospital in an ambulance.

*Examination.*—A careful physical examination was made by Dr. Du Bois; only the important findings are here reported. The patient was a well-nourished but rather undersized girl of 15. She lay doubled up on her right side, unconscious, but could be roused enough to give her name and age. When left alone she was perfectly quiet; when disturbed she resisted a little with her hands. She was cyanotic, not anemic or dyspneic. She looked very seriously ill.

*Tongue:* Moist and coated with white fur and covered with thick mucus.

*Eyes:* Pupils small, equal, reacted slightly; no ocular palsies, no nystagmus. On the ocular and palpebral conjunctiva were several small petechial spots.

*Neck:* Not stiff; when moved forward of the median line, the patient was aroused and resisted a little.

*Heart:* No enlargement. Action 140 to the minute, regular, of good force. No murmurs heard.

*Pulses:* Equal, corresponded to apex, small, soft, walls of vessel not felt.

The other viscera apparently normal.

*Extremities:* Upper, no paralysis. Lower, no paralysis. No edema, knee-jerks normal. *Kernig:* There was slight resistance when the leg was fully extended on the flexed thigh.

*Surface:* Over the whole surface, but most abundant on the abdomen, was a profuse eruption of irregular purpuric (purple) spots varying in size from a pin-point to 2 cm. in diameter. They occurred in the face, conjunctivæ and pharynx.

*Clinical Diagnosis:* Epidemic cerebrospinal meningitis, fulminant.

*Course of Disease.*—October 7: Temperature 100 to 101. Lumbar puncture, at 9 p. m., October 5, withdrew normal fluid at normal pressure. High leucocytosis. Urine normal. Patient was very noisy and irrational, at times unusually bright. She seemed somewhat hysterical. She could repeat her multiplication tables with few mistakes. The neck seemed a little stiff. No new spots appeared on the skin; the old ones were a little darker and were now a reddish purple, edges indistinctly defined; many of them had gray centers which seemed to be on the point of sloughing. These were slightly raised and distinctly tender.

There were about 20 such spots on the buttocks, 3 on the right hand, 1 on the chin, 1 on the left shoulder, about 20 on the thighs and legs. There was a crop of herpes on the lips.

October 9: The patient was a little quieter; she was obstreperous but perfectly rational. She had no headache. The herpes vesicles on the lips were more marked. The tongue was slightly coated and red at the edges. The petechial spots on the soft palate were now white and sloughing. The right eye showed a severe conjunctivitis, the whole conjunctiva being intensely injected and swollen. The left conjunctiva was normal. The hearing was acute. The neck was a little stiff. The joints were held somewhat stiff, but not tender. Kernig: The patient complained of great pain when an attempt was made to extend the leg beyond 135 degrees. No new petechial spots had appeared. The spots which two days previously showed gray centers were indurated and tender, not broken down and seemed to be dissolving. Lumbar puncture October 8 was unsuccessful, only blood being obtained after several punctures.

October 11: The temperature rose to 102.5. The patient was quieter, and perfectly rational. She had pain in the feet and abdomen. Leucocytes continued high. Lumbar puncture withdrew only a small amount of dark clotted blood. Conjunctivitis in the right eye increased rapidly. October 10 it was found that the cornea was hazy, iris blurred and markings indistinct and that the anterior chamber contained much yellowish exudate. The eye was examined by Dr. F. J. Parker, who made the diagnosis of hemorrhage in the eye with iridocyclitis. This day there was no facial paralysis; hearing was acute; there was no headache; the neck was stiff and could not be bent beyond the midline. The mouth showed two small ulcers where the petechial spots had been located. Over the outer aspect of each ankle there was redness, slight tenderness, increased local heat. The right foot was more tender. All the smaller purpuric spots on the skin had practically disappeared and there were now only faint purplish mottlings. A few of the larger ones were still indurated with gray sloughing centers. The skin was not broken down over any of them. All the joints were stiff and a little painful on movement.

October 13: Temperature was 101 to 103. Meningococci were found in the blood culture taken October 9. The patient was very noisy and at times irrational. The whole anterior chamber of the eye was hazy; the exudate did not seem increased; the conjunctivæ not so much inflamed. The neck was very stiff. The spots were fading; there were now about fifty left. A few contained pus; none were broken down. Kernig: The legs could be extended to within 45 degrees of a straight line. The knee-jerks were faint. The feet were no longer swollen. The general condition was not so good. The patient talked incessantly in a loud shrieking voice. The cultures obtained from the blood were submitted to Dr. Flexner who corroborated the diagnosis.

October 14: On October 13 lumbar puncture in the third lumbar space, withdrew about 20 c.c. of claret-colored fluid not under increased pressure. It did not look purulent and no organisms or pus cells were found. Twenty c.c. of Flexner's meningitis serum were injected into the spinal canal and 25 c.c. more were given in an intravenous infusion just after a blood culture had been made. This latter proved sterile. Following this the temperature rose to 104.6 but fell a little to 103.4 on the morning of October 14. The patient was still very noisy. She did not seem irrational and could multiply 6 by 6 and 5 by 8 correctly. She seemed hyperesthetic when touched. The neck was not quite so stiff as on the 13th. The throat was clear except for white patches on the left tonsil and right cheek, where petechial patches were located. Right eye: Conjunctival sac deeply injected and swollen, although not so much as three days previously. The cornea was cloudy, the

pupil moderately dilated, iris cloudy. There was a white patch apparently in the middle of the anterior chamber. Knee-jerks active. Sensation: Patient could distinguish accurately between sharp and blunt end of a pin. Kernig: The right leg could be extended to within 35 degrees of a straight line. The left could be extended to almost a straight line. The joints were no longer stiff. The feet were only a little tender. No paralysis; eyes looked in every direction; the tongue did not deviate. General condition a little better.

October 19: This was the fifteenth day since the onset. The patient was improving steadily. On October 17 30 c.c. of Flexner's serum was given subcutaneously. After that the temperature fell from 101.5 to 100. The leucocytes were decreasing. The patient was very noisy and irrational at times, but this seemed to be largely hysterical. This morning she was rational and laughed and complained of no pain. The eye was still hazy and there was an opacity apparently on the anterior surface of the lens, but this was decreasing in size. The pupil was dilated and a little irregular. The conjunctivitis was less marked.

October 20: Lumbar puncture gave clear fluid at first; later a little blood; pressure was low; fluid rose in tube to 11 cm., and when patient was crying ranged between 11 and 27 cm., returning to 11 cm. when patient became quiet.

November 5: The temperature remained below 100. The patient was up in a chair without fatigue; had no headache, no earache, no pain in the eye. Vision with left eye seemed normal, with right eye absent. Intraocular tension was very low, pupil dilated and a little irregular. Far back in the posterior chamber was a gray mass. Iris was dull, conjunctivae slightly injected. Sloughs on tonsils and inside of cheeks had entirely healed. Otherwise the patient was well.

November 25: The patient had made a steady improvement; was now able to be up and about. The right eye was still blind. Beyond a moderate anemia the patient showed no other consequence of her illness.

TABLE OF LEUCOCYTE COUNTS, LUMBAR PUNCTURES, ETC.

Date.	Day of Disease.	Leucocytes.	Hour.	
10/ 5....	1		12:30 a. m.	Onset with vomiting.
10/ 5....	1		9 p. m.	Lumbar puncture—clear fluid.
10/ 6....	2	27,500		
10/ 8....	2	28,600	5:20 p. m.	Lumbar puncture—small amt. blood.
10/ 9....	5		3 p. m.	Lumbar puncture—dark blood clot.
10/ 9....	5		5:20 p. m.	Blood culture—pure cult. meningococci.
10/12....	8	19,400		
10/13....	9		4 p. m.	Lumbar punc.—clear blood-tinged fluid.
			4:15 p. m.	Flexner's serum—20 c.c. intradurally.
			4:30 p. m.	Blood culture—sterile.
			4:50 p. m.	Flexner's serum—25 c.c. intravenously.
10/14....	10	18,000	5:15 p. m.	Flexner's serum, 30 c.c. subcutaneously.
		18,200		
10/15....	11	18,400		
10/16....	12	13,800		
10/17....	13	13,100	2:30 p. m.	Flexner's serum, 30 c.c. subcutaneously.
10/18....	14	13,000		
10/19....	15	9,000		
10/20....	16	11,100	6:25 p. m.	Lumbar puncture—clear fluid.
10/21....	17	10,400		
10/22....	18	9,800		
10/24....	20	10,100		
10/26....	22	23,500		
10/27....	23	17,600		
10/30....	26	14,100		
11/ 2....	29	14,700		

## DIFFERENTIAL COUNTS OF LEUCOCYTES

	Oct. 6.	Oct. 12.	Daily Percentages.		Oct. 27.
			Oct. 14.	Oct. 17.	
Polynuclears .....	82.	72.7	61.3	78.*	64.
Transitionals .....	3.7	2.7	.2	2.3	1.3
Large mononuclears .....	8.	9.6			
Lymphocytes .....	6.	15.	27.8	19.	34.
Basophiles .....	.3	0.	1.	0.7	0.
Eosinophiles .....	0.	0.	.7	0.7	0.7
Platelets .....	few	few	few	few	few

\*300 leucocytes counted.

## PATHOLOGICAL LABORATORY REPORTS

- Oct. 9—Blood culture on broth. Pure culture of meningococcus (Cecil).  
 Oct. 13—Blood culture on broth. Both sterile.  
 Oct. 12—Smears from right conjunctiva. Pus: fibrin. Very few micro-organisms (Meakins).  
 Oct. 11—Culture from right eye (blood agar). Smears show mucus and pus; Gram cocci and bacilli. Cultures give *Staphylococcus albus* and *B. xerosis* (Cecil).  
 Oct. 13—Smears and cultures from purpuric spot (sheep serum agar). Smears show a few scattered pus cells but no bacteria. Cultures sterile (Cecil).  
 Oct. 12—Smears from vagina. Many organisms and epithelial cells (Meakins).  
 Oct. 13—Smears from posterior fornix of vagina, 12 hrs. after douche. Moderate number of pus cells negative (Cecil).  
 Oct. 5—Spinal fluid. Twenty c.c. perfectly clear fluid. No sediment. No coagulum. Smears negative. Culture sterile (Cecil).  
 Oct. 9—Spinal fluid. About 1 c.c. of serum containing a large blood clot. Smears show blood but no pus. No micro-organisms. Cultures sterile (Cecil).  
 Oct. 13—Spinal fluid. 15 c.c. of blood-tinged fluid. Dark red sediment. Smears show blood but no pus. Cultures sterile (Cecil).  
 Oct. 16—Spinal fluid. 25 c.c. blood tinged. Dark red coagulum. Smears show blood, no pus, no bacteria. Cultures sterile (Cecil).  
 Oct. 20—Spinal fluid. 30 c.c. of clear colorless fluid. No coagulum. No sediment. Smears entirely negative. Cultures sterile (Cecil).  
 Oct. 7.—Urine, 24 hours; alkaline; sp. gr., 1014; no albumin, no sugar, no indican. Quantity 1076 c.c. Uric acid, 0.403 gm. Total phosphates, 2.09 gm. (Granat).

As it is established that meningococcus septicemia is possible without meningitis, the question naturally arises whether the case here recorded belongs in that category.

On the admission of the patient the clinical diagnosis was entered as cerebrospinal meningitis. In the light of the negative lumbar puncture, and the marked hemorrhagic symptoms, together with the absence of conclusive signs of meningitis, purpura hemorrhagica was later suggested. The blood culture cleared up the question of diagnosis. We are not yet entirely satisfied as to the presence of meningitis. On admission the patient was stuporous, but without notable stiffness of the neck or extremities, or other definite evidences of invasion of the cord or brain. Later the stupor gave place to a fretful and irritable mental condition, in which the patient appears to have been mentally

more active than since her recovery, with definite rigidity of the neck, Kernig's sign and general hyperesthesia. The apparent Kernig may have been due to the involvement of the knees. Rigidity of the neck is seen, as all know, in conditions free from meningitis, such as typhoid fever or pneumonia, and Kernig's sign is not by any means limited to meningitis, but taken together these symptoms certainly point to a definite involvement of the cord. On the other hand, five successive lumbar punctures yielded a quantity of cerebrospinal fluid which must have shown the meningococcus if the cord had been involved in the inflammatory process; on each occasion, however, the fluid proved sterile.

The chief source of cerebrospinal fluid, it is agreed, is the chorioid plexus. The maintenance of a normal supply of the fluid about the cord implies an uninterrupted circulation of the fluid from the ventricles of the brain through the foramen of Magendie to the spinal canal. The quantities of fluid obtained at lumbar puncture, 20 c.c., 1 c.c., 15 c.c., 25 c.c. and 30 c.c. seem to show clearly that there was no obstruction to the normal course of the fluid, or the later tapplings would have been "dry." The inability to obtain more than 1 c.c. on the second puncture was evidently due to the presence of considerable blood at the usual point of puncture. When the needle was later inserted in the third lumbar space the larger quantities were readily obtained. The normal pressure reading obtained at the puncture of October 20 is another strong argument for the presence of normal circulatory conditions in the spinal canal. Involvement of the cord can, therefore, it would seem, be excluded.

The possibility remains that there was a meningitis limited to a part or the whole of the cerebral surface but cut off from connection with the surface of the cord, or of such nature that the usual purulent exudate was lacking. For either of these suppositions no support can be found in the pathology of epidemic cerebrospinal meningitis. Involvement of the cord seems always to be found. In the thirty-five autopsies of Councilman, Mallory and Wright the process always invaded the surface of the cord to some extent, and so far as I can learn such extension of the disease is constant. It is well known that in the early stages of the meningitis the pathologic process may be limited to a congestion of the pia-arachnoid with very little exudation, so that an early lumbar puncture may be negative, but in cases protracted for two weeks or more the typical exudate always appears and the spinal fluid sooner or later shows pus and cocci. It is also true that in a series of punctures one or more may be sterile while the others yield the specific organism, but I can find no reference to an experience such as ours, in the presence of a definite meningitis.

The involvement of the eye to the extent described may be regarded as good evidence of the presence of a meningitis. Councilman, Mallory

and Wright report the histologic examination of two eyes presenting the lesions of iridocyclitis as a complication of cerebrospinal meningitis. In one of these they were able to trace the meningococci along the optic sheaths from the brain to the eye, apparently showing that the inflammation of the eye developed by direct extension from the pia-arachnoid. On the other hand, it must be granted that, the organism being present in the blood, it may readily lodge in any part of the body, affecting the eye quite as easily as the joints.

In view of the conflict of evidence it is impossible to reach an entirely satisfactory conclusion, but it seems easier to explain the clinical symptoms as expressions of a general bacteriemia than to assume the presence of a meningitis in the face of the strong evidence against it. In the title of this report, however, only the proved facts have been stated: a meningococcus septicemia with sterile cerebrospinal fluid.

Apart from the difficult problem of diagnosis the case here reported presents interesting features.

The eruption was a very remarkable one in the size of the petechial areas and the sloughing which took place in the centers of the larger patches.

In Salomon's and Liebermeister's patients also the eruptions were striking features of the illness. They describe the lesions as a roseola, resembling that of typhoid, or like flea-bites. The multiform character of the eruptions seen in cerebrospinal meningitis is too well known to merit comment. It is perhaps suggestive that in those cases in which, as in the present case, the meningococcus was present in the blood, the eruptions were so marked. Is the eruption in these cases the expression of an embolic or thrombotic process set up by the lodgment of the specific organism in the capillaries of the skin? It is of interest that in Andrewes' cases, as well as in the one here recorded, the appearance of the eruption marked the onset of the disease; and if we take this view of its pathogenesis, we have another argument for primary blood infection in the case just reported.

Liebermeister notes that his case enables us to determine the accessory symptoms of meningitis—that is, those due to the general infection and not to the focal lesion; and he enumerates these as hectic fever, pain in the joints, and contractions of muscles, slight mental dullness, emaciation and roseola-like rash. The fever, eruption and arthritis with resulting muscular contractions are all found in Salomon's case, as well as the one here reported.

All but two of the ten cases in which Elser found the meningococcus in the blood proved fatal; and in almost all the other cases of menin-



gococcus septicemia here mentioned the outcome was the same. It is therefore notable that the patient whose case has just been recorded made a prompt recovery. Liebermeister's was in the hospital for four months, Salomon's for more than that period. The patient here reported was quite well at the end of one month, and is now, at the end of the second, able to return home at any time she wishes. In fact, whether she had meningitis or not, the rapidity of her recovery was remarkable, all the more so if it be granted that she had meningitis as well as the blood infection. In what degree this rapidity of recovery was determined by the energetic administration of the Flexner serum one can not say, but from clinical observation we (the hospital staff) were satisfied that the serum played an important part in the improvement of the patient.

It has been noted that the blood culture taken immediately before the first dose of serum, as well as those cultures made later, all proved sterile, but it would not be justifiable to assume from this fact that the organisms had altogether disappeared from the blood before the introduction of the serum. The efficacy of the serum has been too well proved in cases of meningitis to make it desirable to pursue this point further.

Special mention must finally be made of the ocular complication. Beginning as a conjunctivitis, this quickly developed into a panophthalmitis, with hemorrhage in the vitreous humor. The affection increased rapidly and seemed to threaten the destruction of the eye. Following the use of the serum, improvement began which, in Dr. Parker's opinion, was most remarkable. From that time on the condition changed rapidly for the better, and the preservation of the eye, though without vision, seems assured. Dr. Parker considered the condition as typical of metastatic infective inflammation of the eye. The cases of Tooke, Wintersteiner, and Duval were apparently of like kind. It is notable that these were all fatal cases. The complication is not a frequent one and the cases just mentioned are the only ones in which Duval could find mention of it. Koplik speaks of it as a complication of fatal cases only. The fortunate recovery of our patient is, therefore, all the more noteworthy and constitutes a strong argument for the efficacy of the serum.

The cases here grouped together fairly establish the possibility of a primary meningococcus septicemia and suggest the clinical picture. Doubtless with more frequent bacteriologic examination of the blood during life we shall find such cases not very uncommon.

My thanks are due to Dr. Kinnicutt for the privilege of reporting this case, and also to the house physician, Dr. DuBois, for the very careful clinical notes recorded from day to day.

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# THE OCCURRENCE OF FAT IN THE ISLANDS OF LANGERHANS \*

DOUGLAS SYMMERS.

NEW YORK

From the pathologic standpoint perhaps the chief interest in the pancreas lies in its relationship to diabetes. The association of true diabetes with diseases of the pancreas is not an infrequent one and was noted by Cowley as early as 1788. It remained, however, for Minkowski and von Mering,<sup>1</sup> in 1889, to establish a definite anatomic basis for pancreatic diabetes. These investigators extirpated the whole of the pancreas from certain animals and succeeded in reproducing the typical manifestations of diabetes as observed in man, and their conclusions have been confirmed since by many others.

In 1901 Opie<sup>2</sup> contributed a noteworthy contribution to the pathologic histology of diabetes, directing attention especially to changes in the islands of Langerhans. The structure and location of these islands, the rich supply of capillary vessels in them, the intimate relationship of the cells to the capillary network and the absence of ducts favor the view that these bodies are comparable to the ductless glands. It is assumed that they elaborate an internal secretion that bears an important relation to the metabolism of the carbohydrates. This hypothesis is supported by considerable evidence.

For example, in certain lesions of the liver characterized by destruction of the parenchyma, the islands of Langerhans have been found tremendously enlarged. In Warthin's case<sup>3</sup> there was a primary adenocarcinoma of the gall bladder with extensive metastases in the liver. Ohlmacher<sup>4</sup> reports an exactly similar case and, in addition, a con-

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\*From the Pathological Laboratory of the New York Hospital.

1. Von Mering (J.) and Minkowski (O.): Diabetes mellitus nach Pankreas-exstirpation. *Arch. f. exper. Path. u. Pharmacol.*, 1889, xxvi, 371. Minkowski (O.): Untersuchungen uber den Diabetes mellitus nach Exstirpation des Pankreas. *Ibid.*, 1893, xxxi, 85.

2. Opie (E. L.): The relation of chronic interstitial pancreatitis to the islands of Langerhans and to diabetes mellitus. *Jour. Exper. Med.*, 1901, v, 397.

3. Warthin (A. S.): A case of primary adenocarcinoma of the gall bladder, with secondaries in both adrenals . . . and hypertrophy of the pancreas. *Philadelphia Med. Jour.*, 1900, vi, 38.

4. Ohlmacher (J. C.): The relation of the islands of Langerhans to diseases of the liver, with special reference to carbohydrate metabolism. *Am. Jour. Med. Sc.*, 1904, new series. cxxviii, 287.

siderable number of other cases, such as cirrhosis, chronic passive congestion, etc. I have observed the same enlargement of the islands of Langerhans<sup>5</sup> in the pancreas of a non-diabetic individual who died from an acute exacerbation of a subacute diffuse hepatitis, and quite often moderate hypertrophy of the islands associated with advanced brown atrophy of the liver is observed in senile individuals. Ohlmacher suggests that the insular changes accompanying hepatic lesions are to be explained on the ground that the islands enlarge in an attempt to compensate for the limitation of the carbohydrate-burning function of the liver cells.

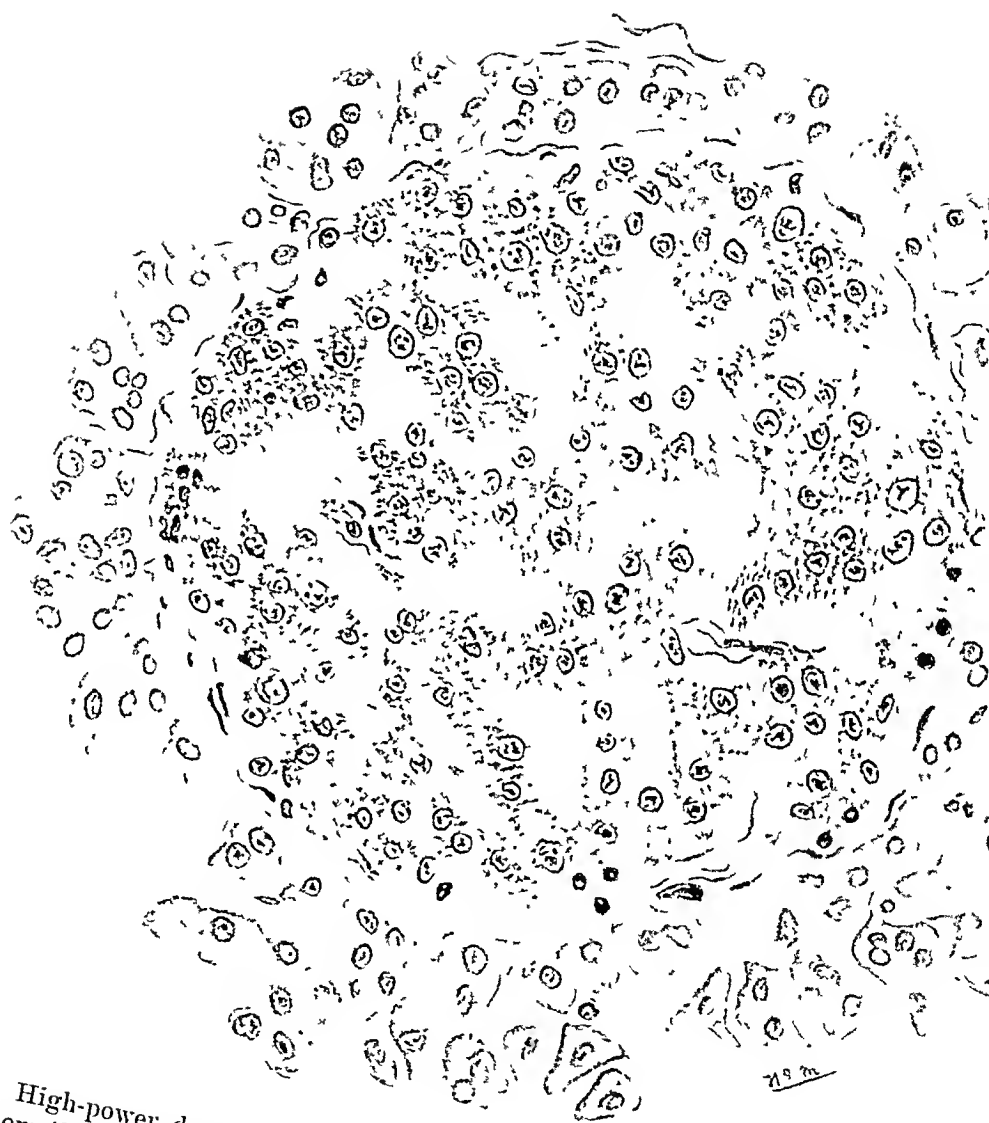
The functional importance of the islands of Langerhans in carbohydrate metabolism is, furthermore, suggested experimentally. If the main duct of the pancreas be ligated, the whole of the part of the gland that is drained by its radicles atrophies and disappears, while the islands remain intact and no sugar appears in the urine (Ssobolew). If, however, the whole of the pancreas be now removed, glycosuria supervenes. If, on the other hand, the pancreas be allowed to remain in the body the islands eventually become involved in the sclerotic process and sugar appears in the urine.

Opie called attention<sup>2</sup> to two varieties of chronic pancreatitis—an interlobular and an interacinar. In the first-named lesion the islands of Langerhans are affected only when the sclerosis becomes extreme. In eleven such cases diabetes was present in one instance only and was mild in degree. In this case the islands were involved. The second variety is characterized by diffuse invasion of the lobules by connective tissue and by definite anatomic alterations in the islands. In such cases diabetes is present.

Opie's observations have been amply confirmed by several investigators. But numbers of cases have been recorded in which the islands of Langerhans appeared microscopically to be unaffected. Karakascheff, for example,<sup>6</sup> examined the pancreas in 11 cases of diabetes. In 4 instances the patients had died in coma. In no case did he find sufficiently marked changes in the islands to account for the existence of diabetes. In some cases, on the contrary, the islands were less sharply defined than normally and were distinctly hypertrophied. The cells at the periphery showed an acinus-like formation resembling that of the gland substance

5. Symmers (D.): *Am. Jour. Med. Sc.*, 1908, cxxxv, 251.

6. Karakascheff: *Centralbl. f. allg. Path.*, 1904, xv, 992. See also Vincent (S.) and Thompson (F. D.): *The islets of Langerhans in the vertebrate pancreas*. *Proc. Physiol. Soc.*, London, 1906, p. xxvii. *Jour. Physiol.*, 1906, xxxiv, 27; 1907, 35, 95.



High-power drawing showing the presence of fat in an island of Langerhans. From the pancreas of an alcoholic male subject, aged 63, who died from an injury to the skull. Stained with Sudan III.



proper and zymogen granules appeared in them. Karakascheff's conclusion is that the islands probably have no specific relationship to diabetes, but that they represent incompletely developed parts of the gland, the cells of which are capable of being transformed into parenchyma cells to compensate for those that have been rendered useless. Hansemann,<sup>7</sup> as a result of the examination of the pancreas in 45 cases of diabetes, came to the conclusion that the islands of Langerhans "have nothing to do with the production of diabetes, or, at most, their connection there- with is very remote." Similar opinions have been expressed by Herx- heimer and Dieckhoff. In a series of cases collected from the literature and analyzed by Sauerbeck<sup>8</sup> the islands of Langerhans were found to be unchanged in 36, slightly changed in 42 and greatly changed in 43. In this connection it is interesting to recall that M. B. Schmidt<sup>9</sup> has ob- served an increase in the size and number of the islands of Langerhans in a diabetic individual 55 years of age. MacCallum<sup>10</sup> has reported a similar case in a diabetic boy 10 years of age. It is also interesting to note that Lazarus<sup>11</sup> has produced very remarkable hyperplastic changes in the islands of Langerhans of guinea-pigs by the prolonged adminis- tration of phloridzin and adrenalin.

Similarly, there are authentic cases of total destruction of the pan- creas, unaccompanied by diabetes. Thus Hansemann<sup>12</sup> several times has seen the entire substance of the organ transformed into tumor tis- sue without the occurrence of sugar in the urine. He describes a form of granular atrophy of the pancreas that stands, he thinks, in close relationship to diabetes. In order to explain the non-occurrence of dia- betes in those instances in which the pancreas has been entirely converted into cancer, he advances the ingenious hypothesis that the cancer cells themselves exercise that function which, in the normal pancreas, influ- ences the metabolism of the carbohydrates. There are those, however, who prefer to believe that in the conditions in question the function of the main pancreas is transferred to pancreatic rudiments to be found in various parts of the abdomen. The literature contains frequent ref- erences to the discovery of such rudiments, and, as a matter of fact, they are not uncommonly to be observed in the walls of the stomach and in-

7. Hansemann: *Centralbl. f. allg. Path.*, 1904, xv, 552.
8. Sauerbeck: *Virchow's Arch. f. path. Anat., Suppl. Heft*, 1904, clxxvii, 1.
9. Schmidt (W. B.): *München. med. Wehnschr.*, 1902, xl, 51.
10. MacCallum: *Ann. Jour. Med. Sc.*, 1907, cxxiii, 432.
11. Lazarus: *München. med. Wehnschr.*, 1907, xlv, 2222.
12. Hansemann: *Ztschr. f. klin. Med.*, 1894, xxvi, 191. For a concise discus- sion of the relationship between cancer of the pancreas and glycosuria, see Pearce: *Am. Jour. Med. Sc.*, 1904, cxxix, 478.

testines in the routine microscopic examination of these parts. In the course of the latest 150 autopsies I met with accessory pancreases of considerable size in 3 instances. Only one was examined microscopically, and in this well-preserved islands were found. The presence of islands of Langerhans in the rudimentary pancreas has also been demonstrated by Albrecht, Wright, Opie, Thorel, Warthin, Theleman, Müller, Gardiner and others.

Even this cursory review of the more important anatomic facts bearing on the functional significance of the islands of Langerhans is sufficient to indicate that the subject is considerably involved. Otto Cohnheim,<sup>13</sup> however, is responsible for a highly significant contribution to the chemistry of the subject that tends to harmonize and clarify certain apparently contradictory anatomic observations. This investigator obtained extracts of the pancreas and of the muscles of dogs and cats. When glucose was added to either of these extracts independently no change occurred. When, however, the pancreatic and muscle extracts were mixed in certain proportions and glucose was brought into contact with them, this latter substance was split into alcohol and carbonic acid. The addition of an excess of pancreatic extract served to diminish or to retard the reduction of the carbohydrate. According to Cohnheim, the muscles produce a glycolytic substance that is activated by a body produced in the pancreas of the nature of an internal secretion. Working independently of Cohnheim, Rahel-Hirsch<sup>14</sup> announced similar results and, in addition, that extracts of the liver are normally capable of reducing glucose to a certain extent, but that if small amounts of pancreatic extract are added the decomposition is greatly accelerated.

In addition to the facts already stated, it is important to call attention to still another phase of the subject, namely, the occurrence of fat in the islands of Langerhans. The presence of fat in these situations was first recorded by Dogiel,<sup>15</sup> who regarded it as a mark of the functional insignificance and degenerate character of the islands. Some years later the subject was reopened by Stangl,<sup>16</sup> who investigated the fat content of the pancreas at different ages, relying mostly on osmic

13. Cohnheim (Otto): Ueber Kohlehydratverbrennung in den Muskeln und ihre Beeinflussung durch des Pankreas. Ztschr. f. physiol. Chem., 1903, xxxix, 336. Id: Ueber Kohlehydratverbrennung. 2 Mitteilung. Die aktivierende Substanz des Pankreas. Ibid, 1904, xlii, 401.

14. Quoted by Adami: Principles of pathology, ed. 1, Philadelphia, 1908, Lea and Febiger, p. 333.

15. Dogiel: Arch. f. Anat. u. Physiol., 1893, 117.

16. Stangl (E.): Zur Histologie des Pankreas. Wien. klin. Wehnschr., 1901, xiv, 964.

acid as a stain. In a 20 cm. fetus Stangl found certain numbers of fatty granules in the cells of the islands of Langerhans. Elsewhere the pancreas was free from fat. In older fetuses and in new-born infants he was able to detect, in addition to fat particles in the islands, a few small droplets in the outer zone of the gland cells. As the scale of years was ascended this picture became exaggerated until, in very old individuals, fat droplets were found to be distinct and numerous, occurring not only in the gland cells and in the cells of the islands, but also in the centro-acinar cells and in the epithelium of the ducts. Stangl was unable to trace any relationship between the presence of fat and pathologic changes in the gland itself. Weichselbaum and Stangl<sup>17</sup> examined the fat content of the islands of Langerhans in several cases of diabetes mellitus and found it present in excess of the quantities to be expected in non-diabetic individuals of like ages, but, in view of Stangl's independent observations, they did not attach any special importance to the observation.

I have had occasion to study the fat content of the islands of Langerhans from a purely morphologic point of view in a series of 73 unselected autopsies, relying largely on Sudan III as a stain. Sections of the pancreas 10 micromillimeters in thickness were cut on the freezing microtome, passed rapidly through 95 per cent. alcohol and subjected to the action of a saturated solution of Sudan III in 80 per cent. alcohol at a temperature of 37 degrees C. for eighteen to twenty-four hours. At the end of this time they were washed rapidly in 80 per cent. alcohol and then in water and mounted in glycerin, after being counterstained in Böhmer's hematoxylin. In these circumstances the fat appears in two forms, either as very minute golden-red granules or as small droplets, staining a golden red at the periphery and yellowish in the center. The fatty particles may be seen lying in the cytoplasm of the cells, the nuclei occupying their normal positions or being but slightly displaced. When present in excessive quantities, the individual cell body is entirely filled, partly by minute granules, partly by the droplets already described. Viewed under the low power of the microscope the islands stand out as sharply defined bodies presenting a brilliant golden-red color in striking contrast to the blue of the surrounding parenchyma, so that the pathologic nature of the process manifests itself at a glance. Sections stained with hematoxylin and eosin in the usual way and passed through the various alcohols fail to reveal, even under the oil immersion lens, the slightest changes in the cells suggesting the presence of

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17. Weichselbaum u. Stangl: *Wien. klin. Wchnschr.*, 1901, xiv, 968.



fat in their cytoplasm. When present in the cytoplasm, the fat stains readily with osmic acid and responds to the usual microchemical tests.

The 73 subjects varied in age from still-born infants to 69 years and presented at autopsy a great variety of anatomic lesions. In 32 instances the subjects had been long addicted to the use of alcohol. Of this number, 24 (75 per cent.) presented excessive accumulations of fat in the islands of Langerhans. The youngest of these subjects was 38 years of age, nine were between 40 and 50, seven between 50 and 60, and seven between 60 and 70. In the remaining eight subjects (25 per cent.) the islands were either free from fat or fat was present in negligible quantities. Of these subjects two were between 30 and 40 years of age, two between 40 and 50, two between 50 and 60, and one was 68 years of age. In 41 non-alcoholic individuals there was no evidence of fat in the islands or fat was present in entirely negligible quantities; that is to say, one or two minute fatty granules could be made out in an occasional island. These subjects varied in age from a 7<sup>1</sup>/<sub>2</sub> months' fetus to 68 years. Of the 73 subjects, two suffered from advanced diabetes mellitus during life, and in neither instance did the islands of Langerhans contain fat or show pathologic alterations of any description.

It is to be observed that these statements are at variance with certain of those made by Stangl, in that I have never been able to detect the presence of fat in the islands of Langerhans in a single subject below the age of 38, while in the great majority of those subjects in whom it was detected there was an associated history of alcoholism. In this connection it is significant that Stangl's observations were made in a country (Austria) where the use of alcohol is almost universal, even among the growing children, and where sucklings receive it through the medium of the mother's milk, in small quantities at least.<sup>18</sup>

The morphologic observations above outlined assume some degree of significance, I believe, if considered in connection with certain clinical investigations carried out by Strauss and with the general facts already stated bearing on the functional significance of the islands of Langerhans.

It has been determined<sup>19</sup> that a normal individual is capable of assimilating from 150 to 200 grams of glucose in a given length of time. Beyond this amount the organism is intolerant of sugar, and the excess

18. Sollmann: Text-book of pharmacology, ed. 1, Philadelphia, 1901, W. B. Saunders Co., pp. 426 and 443.

19. Moritz: Verhandl. d. x Cong. f. inn. Med., 1891, 492. Von Noorden: Disorders of metabolism and nutrition, English translation, 1905, p. 33. Barringer and Roper: Am. Jour. Med. Sc., 1907, cxxxiii, 842.

is excreted in the urine. Strauss,<sup>20</sup> working in Senator's clinic, took advantage of this knowledge and administered to each of 50 healthy individuals 100 grams of glucose dissolved in water. He failed to note the slightest intolerance in a single instance. On the other hand, 20 individuals suffering from acute alcoholism were similarly treated and sugar appeared in the urine in 14 (70 per cent.) of them. Forty-one individuals belonging in the category of chronic alcoholics were likewise treated and as a result 3 of them were found to be intolerant even of this relatively small dose, sugar appearing in the urine in considerable quantities.

The foregoing observations justify, I believe, the following conclusions:

1. The presence of fat in appreciable amounts in the islands of Langerhans, contrary to certain observations recorded by Stangl, is invariably pathologic.

2. Fat accumulates in these situations in individuals at or beyond middle life in response apparently to certain changes brought about in the cells by the prolonged use of alcohol. Thus, out of 32 alcoholic subjects excessive accumulations of fat were present in the islands of Langerhans in 24 instances (75 per cent.), while in 41 non-alcoholic subjects varying in age from a 7 months' fetus to 68 years the islands were wholly free from fat or occasionally fat was to be made out in isolated islands in entirely negligible quantities.

3. The islands of Langerhans may be completely devoid of fat in genuine diabetes mellitus.

4. There would also seem to be sufficient data to warrant the suggestion that the occurrence of fat in excessive quantities in the islands of Langerhans is a factor in the production both of the intolerance for sugar manifested by alcoholic subjects and of the alimentary glycosuria so frequently to be observed in individuals of this type.

In closing, I wish to thank Dr. Harrison S. Martland for the drawing that accompanies this article.

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20. Strauss: *Deutsch. med. Wehnschr.*, 1897, xviii, 275.

# A METHOD FOR HEMOLYSIS AND AGGLUTINATION TESTS

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NEW YORK

The established methods of testing for agglutination and hemolysis have been developed chiefly in animal experimentation, and their application to work with human blood is encumbered with certain hindrances. In all serum reactions there is great need for control tests. The quantity of blood which it is necessary to take from patients for these tests limits the work to a certain extent and, therefore, interferes with the drawing of definite conclusions.

To overcome these obstacles we have developed a method whereby it is possible to perform a large number of tests with a very small amount of blood. In principle the method is identical with that now used by all investigators in this field. In details of technic it is an application of the method used by Wright in his work with opsonins. It has for its main object the reduction to a minimum of the amount of serum necessary for each test.

To obtain the blood either of two methods may be used. The method in general use consists of aspiration from one of the veins at the bend of the elbow with a small syringe (10 to 15 cubic centimeters' capacity). The syringe must be washed out previously with normal salt solution and the usual aseptic precautions must be observed. One or two cubic centimeters of the blood are put in a tube containing an excess of salt-citrate solution (0.5 per cent. sodium citrate, 0.85 per cent. sodium chlorid). The red blood cells are subsequently centrifugated, washed and made up to any desired percentage suspension in normal saline solution. The remainder of the blood is placed in small slanted test-tubes and the serum allowed to separate by clotting.

The alternative method is reserved for cases in which, for any reason, the taking of blood in the above manner is not allowed or is impossible (as in infants). Blood is obtained by pricking the lobe of the ear rather deeply with a Hagedorn needle. For the red cell suspension the drops of blood are taken up with a dropper and expelled into a tube of salt-citrate solution, centrifuged, washed and made up to the desired per-



Fig. 1.—Method of drawing blood from the finger.

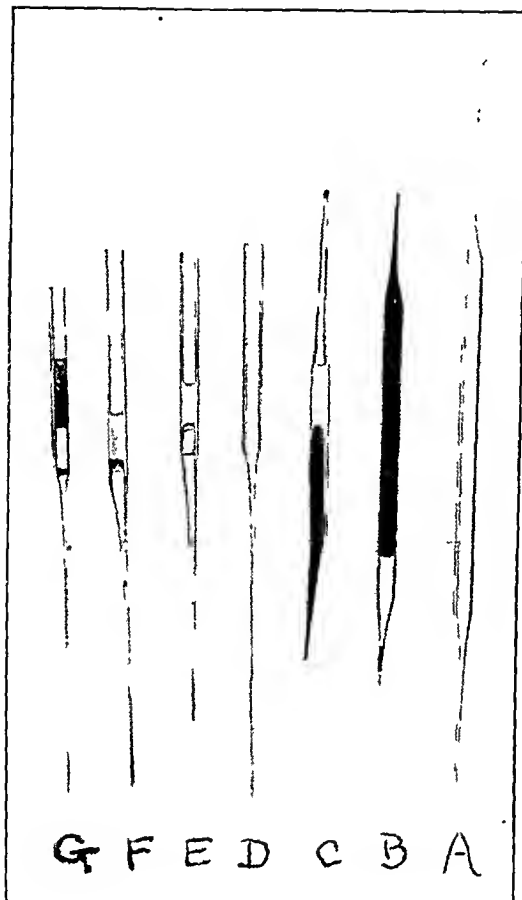


Fig. 2.—Apparatus: A, empty capsule for collecting blood; B, capsule full, lower end sealed, ready for centrifuging; C, capsule centrifuged, serum separated; D, empty pipette for making mixtures; E, pipette, with mixture of red cells and serum which has stood upright for several hours; cells have settled; F, same, showing fairly marked hemolysis; G, same showing very strong hemolysis.

centage. For the serum, capsules, six or seven centimeters long, made of glass tubing about four millimeters in caliber, and drawn out into capillaries at both ends, are used. These capsules fill themselves with blood by capillary action (Fig. 1). When the tube is three-quarters full the unused free capillary end is sealed in a small flame. The blood is allowed to clot and the capsules are centrifuged. After each capsule is nicked with a file it is broken open and the serum can be pipetted off.

For making the mixtures small pipettes (four to five millimeters' caliber), fitted with rubber nipples, are used (Fig. 2). The tips of these pipettes, drawn to a length of two or three inches, are marked at an arbitrary point with a blue pencil. The suspension of erythrocytes is drawn up to the mark. By drawing this a little farther into the pipette one allows a small bubble of air to enter the tip, and then, in a similar manner, one or more volumes of the serum are drawn into the same pipette. Thus definite proportions of the ingredients can be accurately measured. By running the cell suspension and serum gently up and down in the pipette they become thoroughly mixed. The entire mixture is then drawn up into the body of the pipette and the tip is sealed in a flame. The pipettes may be kept upright by sticking them into a tumbler of sand. These narrow tubes serve in every detail the purposes of the larger test-tubes generally used.

The glassware should be absolutely clean and dry, but need not generally be sterile.

As to the time and manner of incubation and observation the well-established rules are followed. In studying hemolysis with human red blood cells, it is essential that the mixtures be made within twelve or at most twenty-four hours of the time of collecting the blood. Otherwise the cells become abnormally vulnerable to hemolytic agents. At the end of the two hours in the thermostat most of the cells have usually settled to the bottom, and pronounced hemolysis can be seen. For finer grades of hemolysis it is usually necessary to allow the tubes to stand twelve to twenty-four hours (in the ice-box).\*

Agglutination (which, when it occurs, is rather prompt) can be readily observed in the gross by the clumping and sedimentation of the erythrocytes.

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\*When it is desired to make comparative tests as to the intensity of hemolysis, the total amount (as well as the proportions) in each test ought to be the same. In this case it is easy to calibrate any number of pipettes by simply transferring a small drop of fluid (normal salt solution) from the tip of one to the tip of another.

The importance that direct blood transfusion has recently assumed, and the necessity of testing for hemolysis as well as agglutination before each transfusion, should make this method one of clinical value. The ease and rapidity with which experiments can be made by this method make it of value in scientific work. The results obtained have been compared in parallel tests with those of the standard method and found to be identical.

# PAPILLOMA OF THE CHORIOID PLEXUS WITH HYDROCEPHALUS

## REPORT OF A CASE

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There are a few reports of the careful examination of growths from the ependyma of the ventricles or the chorioid plexus, growths largely patterned after this vascular structure and variously interpreted as instances of hyperplasia, papilloma or carcinoma. It is a matter of some historical interest that Jacobson, in the seventh edition of Hilton's classical work, "Rest and Pain," mentions a papillary tumor in the floor of the fourth ventricle with occlusion of that cavity and a consequent enormous dilatation of the lateral ventricle appearing externally on the brain like a cyst. This observation and that of Douty<sup>1</sup> have been omitted by several writers who have published otherwise fairly comprehensive reviews of the literature bearing on these growths, accompanying reports of additional cases.

Douty described the occurrence, in a seventeen-year-old boy, of a tumor resembling a large purple mulberry, soft and fragile and attached to the roof of the fourth ventricle by two slender pedicles. It completely blocked the flow of cerebrospinal fluid and caused hydrocephalus, a sequence often observed in connection with these tumors. Other reports by Bruch<sup>2</sup> and Guérard<sup>3</sup> have not been included in the bibliographies of several writers,<sup>4</sup> although their descriptions leave very little room for doubt that the growths examined were of this nature. Bruch first saw the growth which he considered as a papillary carcinoma (*Zottengeschwulst*) when the medulla was sectioned. It lay in the middle of the fourth ventricle and had closed the aqueduct of Sylvius and pressed the vermis upward. It possessed a villous exterior, was fragile and was likened by Bruch to a baked apple in appearance; the ventricles were enlarged. Guérard's account concerned a tumor the size of a hen's egg in the posterior horn of the right lateral ventricle, an

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1. Douty: Brain, 1885-1886, viii, 409.

2. Bruch: Arch. f. physiol. Heil., 1885, xiv, 77.

3. Guérard: Bull. Soc. anat. de Paris, 1850, viii, 211.

4. Cimbal: Virchow's Arch. f. path. Anat., 1901, clxvi, 289.



unexpected discovery in the examination of the body of a girl of three years who died of measles. Anteriorly it was continuous with the chorioid plexus, and Guérard believed that it possessed the same structure as the plexus.<sup>5</sup>

Lebert<sup>6</sup> subsequently referred to this growth as an erectile tumor.

The consideration given this form of brain tumor by Brüchanow<sup>7</sup> is the one most commonly referred to in the recent literature. Since that appeared, Saxer<sup>8</sup> has reviewed the literature, re-examined several of the previously described tumors and added new observations.

Although these ependymal papillary neoplasms are perhaps not the rarest tumors which occur primarily in the brain, they are, nevertheless, comparatively uncommon, and, as is the case with so many of the rare forms of disease, the early history of the observation of these growths will probably always remain somewhat indefinite from the incomplete description or the lack of adequate histologic examination accompanying the older reports. Some idea of their rarity is afforded by the fact that Brüchanow, in 1898, mentioned but five cases, details of which were published before the results of his examination of the growth subsequently studied by Saxer.

In addition to the names mentioned, papilloma, carcinoma and hyperplasia of the chorioid plexus, these growths have also been considered as examples of adenoma, adenocarcinoma and perithelioma; Virchow referred to them in connection with the psammomas, and Kaufmann likened the one he examined to an intestinal polyp. In at least two instances these ependymal growths, or portions of them, have been removed by operation.<sup>9</sup>

Most of the descriptions are of growths directly continuous with the chorioid plexus, which they so closely simulate in structure, but they may also originate from the ependyma lining the ventricles. The growths described by Cornil and Ranvier,<sup>10</sup> Ziegler<sup>11</sup> and Selke<sup>12</sup> grew

5. "Sa structure la fait supposer formée par le developpement des vaisseaux des plexus choroïdes qu' on ne peut suivre dans les parois de la masse." p. 214.

6. Lebert: Virchow's Arch. f. path. Anat., 1851, iii. 478.

7. Brüchanow: Prag. med. Wehnschr., 1898, xxiii, 585.

8. Saxaer: Beitr. z. path. Anat. u. z. allg. Path. (Ziegler's), 1902, xxxii, 315.

9. Bielschowsky and Unger: Arch. f. klin. Chir., 1906, lxxxi, 61. Atlee and Mills (Examination by Spiller): Brain tumor with Jacksonian spasm and unilateral paralysis of the vocal cord and late hemiparesis and astereognosis. Jour. Am. Med. Assn., 1907, xlix, 2128.

10. Cornil and Ranvier: Manuel d'histologie pathologique, 1881, i, 703.

11. Ziegler: Lehrbuch der allgemeine und specielle pathologische Anatomie, 1898, ii, 376, 377.

12. Selke: Ueber ein epitheliales Papillom des Gehirns. Inaug. Diss. 1901, Königsberg. Abstr. in Jahresb. u. d. Leist. d. ges. Med.

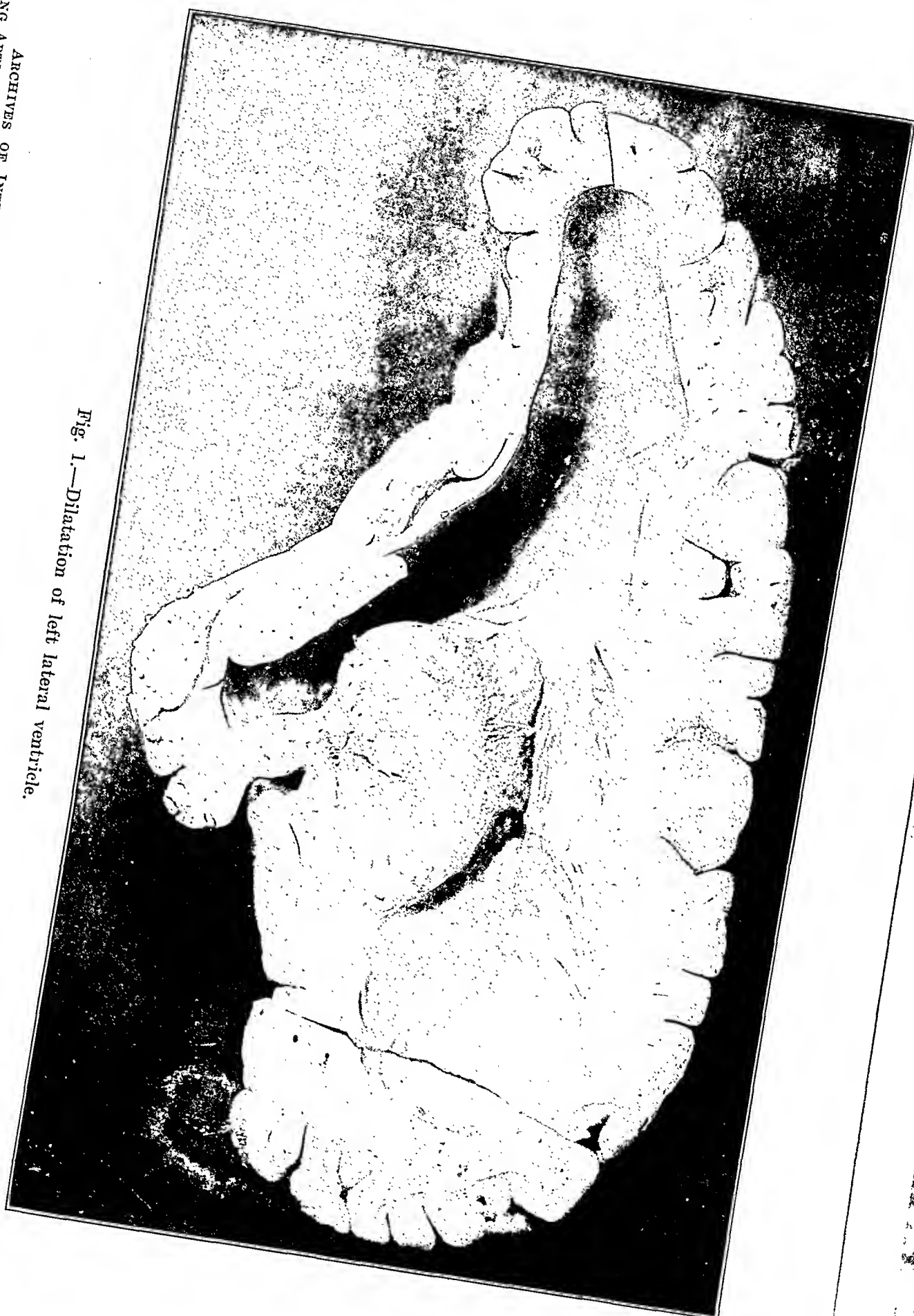


Fig. 1.—Dilatation of left lateral ventricle.



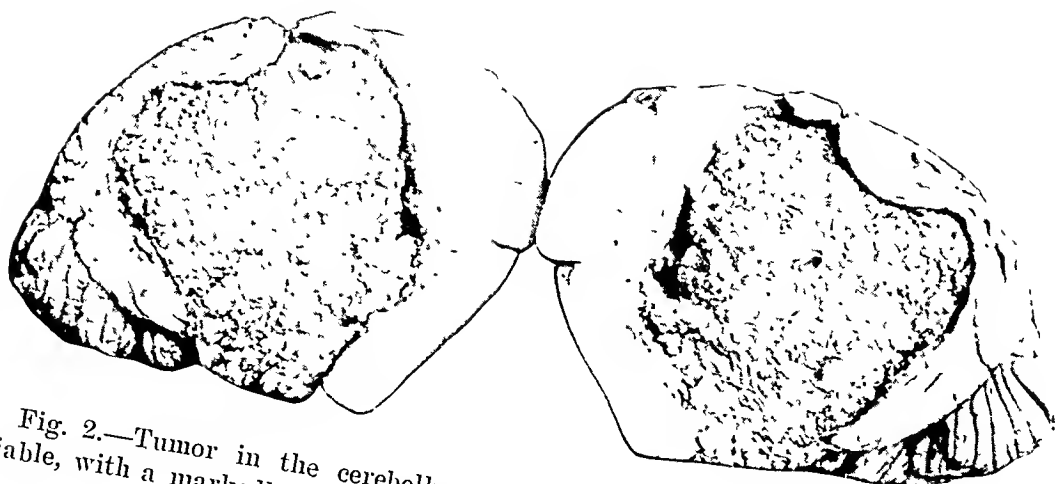


Fig. 2.—Tumor in the cerebellum. A large, globular, pink mass, soft and friable, with a markedly cauliflower-like structure.

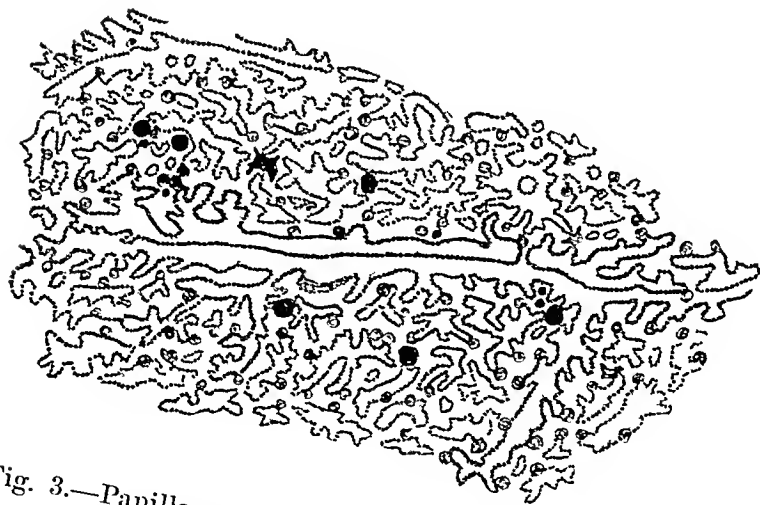


Fig. 3.—Papillary or villous structure of the tumor.



into the lateral ventricles from the third ventricle, but most of them have been found in the fourth ventricle, where they have grown outward or backward, compressing the cerebellum, and produced more or less hydrocephalus by blocking the flow of the cerebrospinal fluid.

The reports of greatest interest from the standpoint of the name these tumors should have and the accompanying conception as to their relative benignancy or malignancy are the accounts of Spät<sup>13</sup> and Bielschowsky and Unger<sup>9</sup> of small secondary tumors disseminated by the cerebrospinal fluid and located on the outside of the brain, imbedded in the cortex and in some instances attached to the pia by slender vessel-bearing strands of tissue. Spät found three such secondary tumors; Bielschowsky and Unger fourteen. The primary tumors do not grow into the adjacent brain tissue, but distend the cavities in which they originate. In these characteristics, growth on the surface and dissemination by the cerebrospinal fluid, these villous papillary carcinomas of the ovary, the latter of which often are responsible for wide-spread so-called peritoneal "carcinosis" by a process of implantation.

On account of the occlusion of the fourth ventricle hydrocephalus has been, as previously stated, observed with most of these growths. Vigouroux<sup>14</sup> describes the amelioration of symptoms following the escape through the nose, which began three years before death, of cerebrospinal fluid from the distended ventricles, as much as 800 c.c. being discharged in twenty-four hours. In the head of the two and one-half-year-old child containing the ependymal growth reported by Brüchanow, the entire palm was required to cover the anterior fontanelle; the coronary, frontal and lambdoid sutures were each 2 cm. wide, the sagittal 8 cm. In connection with the tumor we have to describe, the hydrocephalus was not as marked.

*History.*—The patient, a boy of 11 years, was seen at intervals since he was 1 year old, being the child of parents who employed one of us (S. R. S.) whenever medical attendance was required. When 1½ years old he suffered from a mucous colitis for two months and when 7 he fell from a tree and fractured the left femur. At his birth the labor was normal, and the medical history of the family contains nothing pertinent to the disease causing his death. The fracture mentioned united without noteworthy events but the child remained weak, did not play as actively as the other children, and his weight did not increase proportionately to his growth. When the boy was examined some time subsequent to the fall, on account of the continued impaired health, the enlarged tonsils and indications of adenoids, the only changes found, did not seem sufficient to account for the general weakness and poor health. Following the removal of the

13. Spät: *Aerztl. Intelligenzbl.*, 1883, xxx, 305.

14. Vigouroux: *Rev. neurol.*, 1908, xxvi, 281.

tonsils at the age of nine years there was a temporary improvement and subsequently, under the administration of tonics, cod-liver oil and iron, there were periods of better health followed by relapses, marked by weakness and inactivity. Shortly after the removal of the tonsils a peculiarity of gait was noticed; it was swaying, without any disposition to fall to one side more than the other, unsteady and accompanied by a grasping at surrounding objects for support. No vertigo was complained of at this or any subsequent time; nor was there during the entire illness any headache, rigidity of the neck, vomiting, nystagmus, optic neuritis, disturbance of vision or other ocular symptoms; in fact the absence of such symptoms when it became apparent that the boy's difficulty in walking was due to some lesion of the nervous system, remained puzzling to the last.

Repeated examinations for disturbances of sensation were made, without result; the reflexes and functions of the various sphincters remained normal. An intention tremor in both hands and feet was the next important symptom noticed following the disturbance in walking. It resembled somewhat that observed in multiple sclerosis, differing, however, in not being increased as the desired result was attained. This tremor was in reality an ataxia and symmetrically bilateral; it was not increased when the eyes were closed, and on this symptom mainly the diagnosis of cerebellar disease was made two years before death and two years after the beginning of the failure of health. The ataxia increased, the voluntary muscles atrophied, but the patient was able to walk with assistance until two months before death.

Just when the head began to enlarge it is impossible to state, but the enlargement was first noticed three months before death, and at this time, when the attention of the parents was called to this development, they had not remarked it. The patient remained mentally clear until a few weeks before death. Death was extremely gradual, due, it seemed, to inanition, weakness and the failure to take nourishment of any kind; there was no difficulty in swallowing attributable to paralysis of the muscles concerned; for two weeks before death it was apparent that the end might come at any moment.

*Pathologic Report.*<sup>15</sup>—A complete postmortem examination was not allowed, but the cranium was opened and the brain removed and examined after hardening in 10 per cent. formalin in the usual manner. The body was greatly emaciated, the skin pale; posterior lividity marked and rigor mortis absent, the examination being sixteen hours postmortem and after embalming with axillary vessel injections on both sides. The pupils were equal and dilated; the head large, measuring 60 cm. in its greatest horizontal circumference. On removal of the scalp the skull measured 59 cm. in circumference at the same place. The bones of the calvarium were movable, the sutures not closed by bony union, the bones generally thin, measuring 2 mm. at the thinnest places. The dura was tense and the inner surface of the calvarium was marked in many places by depressions corresponding to the cerebral gyri. The meninges were very edematous and in the region of the chiasma the fluid had been coagulated by the admixture with embalming fluid. The brain was soft and fluctuated. It weighed directly after removal 1880 gm. and one hour after removal 280 gm. of fluid had escaped from it. The brain was enlarged, measuring 19 cm. in length and 16 cm. transversely; it was pale, the convolutions slightly flattened, the sulci tightly closed; the vessels at the base appeared normal.

On the under surface a pinkish growth covered with thin transparent pia loosely adherent to it projected between the cerebellum and medulla, the area of the growth so exposed being circular and 2 cm. in diameter. Sectioning the brain after hardening revealed greatly dilated ventricles, especially the posterior horns

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15. From the Pathological Laboratory of Rush Medical College.

of the lateral ventricles. Each lateral ventricle, it was found, would contain 96 c.c. of water. The foramen of Monro was greatly dilated (Fig. 1) also the third ventricle. Sections of the cerebellum exposed the tumor, the periphery of which projected below as described between the medulla and cerebellum, a tumor measuring 4.2 cm. anteroposteriorly, 4 cm. transversely, and 5.2 cm. from above downward, and replacing practically all of the white substance of the cerebellum as well as the dentate nuclei, the enveloping shell of the cerebellar cortex being reduced to 5 cm. in places (Fig. 2). This tumor completely filled the fourth ventricle and the foramina of Magendie, Keys and Retzius. The aqueduct of Sylvius was the size of a goose-quill. The tumor was directly continuous with the chorioid plexus, which appeared to be larger than normal. Sections of the pons and medulla revealed no gross alterations. Sections prepared for microscopic examination from different portions of a thin slice cut out of the growth where its diameters were greatest were all found to possess a structure, varying in no important details.

"There are slender stalk-shaped, villous, branching and greatly tangled frameworks of connective tissue covered with columnar epithelium arranged for the most part as a single layer (Fig. 3). This framework in most places consists of little more than a vessel surrounded by a basement membrane for the epithelium. The difficulties in the circulation necessarily attending such a structure have resulted, judging by the specimens examined, in surprisingly few alterations, e. g., there is no necrosis; there is, however, considerable edema in many of the branches of this vascular cauliflower-like growth, for in many the vessel is no longer apparent and the space between basement membranes is occupied by granular non-staining material. There is much more of this coagulated serum containing loosened cells between the separate divisions, also a great number of round masses varying in size from that of large lymphocytes to the size of a renal glomerulus, which have a laminated structure and stain intensely with hematoxylin. For the most part these objects lie in the free spaces between the epithelial-covered subdivisions of the growth. Their relation is therefore quite analogous to that which would be possessed by shot of various sizes, buck-shot and bird-shot, for example, to a sponge if they were poured into its meshes. It is also evident that the various subdivisions are not all cylindrical, i. e., branching columns, but that in many places the single divisions are in reality sheet-like, and comparable in arrangement to an intricate infolding of a membrane. The nuclei of the epithelial cells are small and stain intensely, and at numerous points the projecting columnar-shaped eosin-staining cytoplasm is two or three times the diameter of the nuclei in extent. The presence of minute granules staining with hematoxylin, in some instances located within the cells and of somewhat irregular and stellate masses also staining with hematoxylin, suggest an origin for the spherical bodies described in a process of secretion or degeneration of the epithelial cells."

The nature of the tumor—its exceptional size, for usually tumors of this variety are smaller—the hydrocephalus it produced and the absence of symptoms generally produced by brain tumors, constitute the most interesting features of this report. Stewart and Holmes,<sup>16</sup> in summarizing the symptoms in 40 cases of cerebellar tumor, refer to headache, vertigo, nystagmus and optic neuritis as being fairly constant phenomena. That exceptions are occasionally met with is not altogether

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16. Stewart and Holmes: *Brain*, 1904, xxvii, 522.



surprising. Jacobi<sup>17</sup> observed an absence of optic neuritis and ataxia in connection with a cyst of the cerebellum, although headache, vomiting and vertigo were present; Anglade<sup>18</sup> has described general convulsions, which were the only symptoms caused by a cerebellar tumor, and Babinski<sup>19</sup> found a correspondingly restricted syndrome limited to hemiasynergie and hemitremor. The gradual manner in which death took place in the boy afflicted with the papillary tumor we have described is also an exception to the sudden death which is frequently a result not only of tumors in the fourth ventricle, but also from the development of tuberculous and syphilitic lesions in the adjacent structures or the localization and growth in the region of parasitic cysts.<sup>20</sup>

In conclusion it might be pointed out that these proliferations of ependyma, especially those connected with the chorioid plexus, represent a reversion to an embryonic condition and, therefore, toward malignant tumors and are in marked contrast to the ependymal gliomas in which the same cells are differentiated in the production of neuroglia.<sup>8</sup>

100 State Street.

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17. Jacobi: *Jour. Nerv. and Ment. Dis.*, 1906, xxxiii, 385.

18. Anglade: *Rev. neurol.*, 1901, xx, 784.

19. Babinski: *Rev. neurol.*, 1901, xx, 260.

20. See the recent articles by Stern (*Deutsch. Ztschr. f. Nervenhe.*, 1908, xxxiv, 195) and Bassoe (*Multiple ependymal glioma, THE ARCHIVES INT. MED.*, 1908, ii, 194).

# THE INCIDENCE OF GLYCOSURIA AND DIABETES IN NEW YORK CITY BETWEEN 1902 AND 1907

WITH A REPORT OF TWO CASES OF ESSENTIAL PENTOSURIA \*

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There are no statistics that I have been able to find concerning the frequency of glycosuria, and the incidence of its not unusual sequel, diabetes, is calculated chiefly from mortality figures and hospital records. The results so obtained vary greatly. Naunyn says, in his book on diabetes, that almost any figures desired can be selected from various estimates, and that only out of courtesy to the authors does he quote any of them. Osler states, in his "Practice of Medicine," that among 99,000 patients admitted to the medical wards and medical dispensary of the Johns Hopkins Hospital, there were 226 cases of diabetes, or 228 per 100,000 of medical admissions. The last report of mortality statistics by the United States Census Bureau shows, between 1901 and 1905, a yearly average of 11.6 deaths from diabetes per 100,000 of population. These figures show how difficult it is to get any idea as to the actual frequency of diabetes, for many diabetics never enter a hospital ward and many die from other diseases.

The records of one of New York's large insurance companies were very courteously placed at my disposal by the medical director, and from them I have been able to secure reliable information on these points.

There were 71,729 adults examined medically by this company in New York City between 1902 and 1907. They belonged, naturally, to the better social class, which shows, as is generally recognized, a greater incidence of diabetes than does the poorer class of people. Probably 95 per cent. or more of them were men between the ages of 18 and 60, and, of course, they were practically all on a mixed diet (one containing carbohydrates).

The men who showed glucose on one or more examinations numbered 2,043, or 2,840 per 100,000. Of these men 681 showed between 1 and 12 per cent., and 1,362 less than 1 per cent. of sugar. In all these cases the presence of glucose was confirmed by an experienced chemist. If

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\*Read before the Section on Medicine of the New York Academy of Medicine, April 20, 1909.

we consider the presence of 1 or more per cent. of sugar in an office specimen of urine, a criterion of the existence of diabetes, the incidence of diabetes per 100,000 of population would be 950. This criterion of diabetes is rather an arbitrary one, but I feel it is justified for the following reasons:

The diagnosis of diabetes at an early stage is a difficult matter, for very little is known about the beginning of this disease. The diagnosis of a fully-developed case with the marked glycosuria, polyuria, loss of weight, etc., is, of course, easy, but very few of those included in our large group of glycosuric cases were of such a type. We know that diabetics react to small quantities of carbohydrates in their food with a decided glycosuria. Any patient reacting to such a diet with a glycosuria as marked as 1 per cent. is, therefore, under strong suspicion, and is probably diabetic. A reaction of only a trace of sugar would leave us in doubt. In a previous paper,<sup>1</sup> however, Roper and I have shown that of a group of 20 patients with slight glycosuria (less than 1 per cent.) 9 had developed diabetes at the end of five years.

Admitting that the glucose percentage criterion of the existence of diabetes may have led us to include cases not diabetic among the 681 quoted above (which showed 1 per cent. or more of sugar), we have as yet left entirely out of consideration the 1,362 cases of slight glycosuria, many of which are or may become diabetic. Their inclusion would raise the incidence so markedly that our previous error would be negligible.

Just what proportion of cases of slight glycosuria become diabetic is difficult to estimate. Our former paper showed in a small series 45 per cent., which is perhaps too low, as but five years had elapsed since the initial glycosurias of these cases. If we figured that 50 per cent. of such cases became ultimately diabetic, our final figures for the incidence of diabetes in New York City would be 1,895 cases per 100,000 of population.

These figures contrast most surprisingly with all previous estimates, and oblige us to consider this disease as certainly not "rare" or "uncommon."

The lack of definite knowledge concerning the beginning of diabetes has led to a very general idea that a transitory glycosuria is in most cases the warning signal of later diabetic disease.<sup>2</sup> In our previous

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1. Barringer and Roper: The prognosis of spontaneous glycosuria, etc. *Am. Jour. Med. Sc.*, 1907, exxxiii, 842.

2. Von Noorden: Disorders of metabolism and nutrition. Diabetes. English transl., 1905, p. 127.

paper we showed that but 45 per cent. of a group of 20 such cases of slight transitory glycosuria had become diabetic at the end of five years. We assumed, therefore, that there were two types of transitory glycosuria: (1) a type essentially diabetic from the outset, in which sugar recurs, which shows constantly *glycosuria e saccharo*, and in which the patients at the end of five or more years become diabetic; (2) a type, quite harmless, in which sugar does not recur after the first few months, which does not show *glycosuria e saccharo*, except perhaps during the first few months, and in which the patients do not develop diabetes. This idea was quite at variance with existing views.

Our present figures show that there is a much greater incidence of slight glycosuria (1,890 cases per 100,000) than of marked glycosuria, (950 cases per 100,000), and confirm the above assumption in regard to types of transitory glycosuria.

Concerning the onset of diabetes: In our former paper the histories of 9 patients, who formed the diabetic group of glycosuria, showed a gradual change from a slight transitory glycosuria to a persistent glycosuria in five years' time, and suggested naturally that this was the usual mode of development of diabetes. In our present statistics the high incidence of slight glycosuria, about double that of marked glycosuria, leads us to believe that the great majority of diabetic cases begin in this way.

This insidious onset would correspond pathologically to a gradual destruction of the islands of Langerhans by a slowly advancing inter-acinar pancreatitis, which Cecil<sup>3</sup> has shown accompanies 73 per cent. of all cases of diabetes.

There were sixteen men among the 71,729 examined in whose urine the insurance company found pentose. I subsequently visited eleven of these and secured twenty-four-hour specimens of urine. Nine specimens were negative, the subjects evidently having been originally affected with alimentary pentosuria. The insurance company's examinations had been made chiefly during the summer months, and had always shown an absence of pentose on the succeeding day, when a second analysis had been done. The greater consumption during the summer months of fruit, which contains pentosans, explains the origin of these cases.

Two of the men showed pentosuria on repeated examinations.

The first was a dentist, 37 years old, in excellent health. He showed generally, in the twenty-four-hour urine, about 0.5 per cent. of a re-

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3. A study of the pathological anatomy of the pancreas in 90 cases of diabetes mellitus. Jour. Exper. Med., April, 1909.

ducing substance (estimated as dextrose) which was identified as a pentose by means of Bial's test, the spectroscopic reaction, and the melting point of the ozason, between 150 and 155 degrees C.

The second man, a clerk, 17 years old, in good health, showed constantly about 0.3 per cent. of a pentose. I was unable to carry out any metabolism experiments on these subjects or to investigate the members of their families.

#### SUMMARY

1. The incidence of diabetes in New York City reaches the surprising figure of 1,895 cases per 100,000 of population.

2. A large proportion of cases of transient glycosuria are harmless and do not develop into cases of diabetes.

3. Diabetes generally begins as a slight, intermittently appearing glycosuria which gradually becomes more frequent and more marked, until finally it is constantly present.

I am much indebted to Dr. J. C. Roper for the urine analysis of these pentose cases.

34 West Eighty-fourth Street.

# THE MORO AND VON PIRQUET TUBERCULIN REACTIONS

IN ONE HUNDRED AND SEVENTY-ONE CASES \*

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In February, 1908, Moro<sup>1</sup> reported a series of 68 cases in which he had used a tuberculin inunction as a means of demonstrating hypersensitivity to that substance. The salve employed was composed of equal volumes of old tuberculin and anhydrous lanolin. In manifest tuberculosis, the salve reaction and the von Pirquet reaction were positive in 12 cases and negative in 4; in glandular tuberculosis, positive in 6 and negative in 1, while in cases of suspected tuberculosis they were positive in 12 and negative in 8. In 25 cases in which no suspicion of tuberculosis existed, the salve reaction of Moro was positive in 3 cases only, while the von Pirquet was positive 8 times. In addition to these 68 cases, 21 tuberculosis-free children reacted negatively and 4 children with manifest disease positively to the salve. In 30 cases, control inunctions with resorbin and adeps lanæ gave results which were entirely negative with the exception of one. He estimates the positive outcome of his reaction in children free from tuberculosis at 12 per cent. and that of the von Pirquet at 32 per cent.

In view of these results, it seemed advisable to give the tuberculin salve a thorough trial, and consequently it has been used in a series of 171 persons of all ages, including non-suspicious individuals and patients suffering from the various forms of tuberculous disease in their different stages. Von Pirquet tests were made at the same time.

The tuberculin used was old tuberculin, kindly furnished by the Department of Health. Moro mentions the salve as being 50 per cent., but, as Heinemann<sup>2</sup> has pointed out, it is probably nearer 60 per cent. The salve remains efficient for a long time if kept on ice, and we have found that it retained its activity at the end of several months.

The salve is rubbed into the abdomen, chest or any location that is free from eruptions, over an area about 5 cm. in diameter, for one or two

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\*From the Department of Applied Therapeutics, Vanderbilt Clinic, Medical Department of Columbia University (College of Physicians and Surgeons); read at the annual meeting of the Alumni Association of the College of Physicians and Surgeons, Jan. 25, 1909.

1. Moro: München. med. Wehnschr., 1908, iv, 216.

2. Heinemann: München. med. Wehnschr., 1908, iv, 556.

minutes. It is advisable to clean the site of inunction with alcohol, for in a number of cases in which the tests were done in two places on the same individual, the result was more marked where the skin had been previously treated in this way. No protecting dressing is necessary; an amount of salve equal to the size of a buckshot is all that is needed. It is advisable to make a ring around the inuncted area, for two reasons: first, in order to differentiate the reactive papules from sudamina which may be present or may appear in summer; second, as Moro<sup>3</sup> has recently pointed out, the papules may not confine their occurrence to the area over which the salve was applied, but may appear around it as well. This particular peculiarity of the reaction has been noted in these cases at least a dozen times.

The reaction may appear in twenty-four hours, and if it does not develop in forty-eight hours it will probably remain entirely negative. Emmerich<sup>4</sup> has reported one case in which it did not appear until the sixth day. One of the last patients in this series (Hudson Street Hospital, Medical No. 2854) came to the hospital spitting blood. It was impossible to determine whether the hemorrhage came from the stomach or lungs. Tests were applied December 10, and the following day a very intense von Pirquet reaction was noted. On the eleventh day, after the reactions had been forgotten, the patient complained of itching at the site of the inunction, and a very intense macular erythema was observed. Over a corresponding position on the opposite side of the body were a moderate number of scattered papules, similar to those found in the ordinary reactions. There were no lesions elsewhere on the skin and there was no other factor that could have produced an eruption.

Mild reactions appear as papules, acneform in appearance, sometimes white, usually red. In one of these cases the papules were surrounded by a definite red areola. They may vary in number from four or five to fifty. A few are occasionally pustular. In one mild reaction there were many miliary papules, which were extremely difficult to see and easily escaped detection except in the strongest light. Occasionally the lesions are erythematous macules.

Reactions of medium intensity show many more papules, apparently smaller in size the more numerous they become. At times the small papules become vesicular, a few being confluent, the majority discrete.

In intense reactions, the surface treated is covered with innumerable papules; many of these are vesicular, confluent or discrete. Frequently a few of the papules are confluent, and occasionally the majority become

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3. Moro: *München. med. Wehnschr.*, 1908, *lv*, 2025.

4. Emmerich: *München. med. Wehnschr.*, 1908, *lv*, 1066.

fused. The papules are situated on an erythematous base, which may occupy the whole surface treated or be distributed irregularly over that area.

Itching has been described by Moro and occurred in about 20 per cent. of our cases.

Moro<sup>1, 3</sup> has recently drawn attention to the appearance of the reaction on the opposite side of the body corresponding to the site of the inunction. This has been observed twice in this series, in an early case, and in the case previously alluded to, in which the reaction was delayed eleven days. Moro also made a number of experiments in which he rubbed the tuberculin salve on one side of the body and lanolin into the corresponding part on the other side, with the result that both areas reacted. He believes that this phenomenon is to be accounted for by the tuberculin's reaching those parts of the cord which preside over the areas of skin affected by the inunction, and that the reaction is largely vasomotor. One is forced to consider the similarity of this explanation to that generally accepted for zoster, and, indeed, in many instances the appearance of the two conditions is identical.

As a rule, the von Pirquet reaction is fully developed several hours before the Moro, but in one of the cases the Moro developed in twenty-four hours, while the von Pirquet did not appear until the seventh day. In 171 cases the Moro reaction was positive 94 times, the von Pirquet 122 times.

#### NON-TUBERCULOUS GROUP (THIRTY CASES)

In only one case of this group was the Moro reaction positive. The patient was suffering from early tabes dorsalis, and the reactions were tried, in an attempt to verify the observation of Fehsenfeld,<sup>5</sup> Heine-mann,<sup>2</sup> and others before them, that tuberculin hypersensitiveness is in some way connected with the state of the nervous system, and that patients who are the subjects of nerve lesions often present the reactions, although they offer no evidence of past or present tuberculosis. Our results show that  $3\frac{1}{3}$  per cent. of the non-tuberculous give a positive Moro reaction and  $23\frac{1}{3}$  per cent. a positive von Pirquet reaction. The number of cases is, of course, too small to establish the relative sensitiveness of the two tests on the part of the non-tuberculous, but it is interesting to note that the 20 per cent. in favor of the von Pirquet reaction corresponds to the figures furnished by Moro. Of the 399 non-suspicious cases from all sources herein considered, 27.5 per cent. gave a positive Moro test. It is probable that subsequent study would have proved a number of them tuberculous.

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5. Fehsenfeld: München. med. Wchnschr., 1908, lv. 1373.



## TABULATED SUMMARY OF RESULTS IN ONE HUNDRED AND SEVENTY-ONE CASES

Classification of Cases.	Test.	Posi- tive.	Nega- tive.
Tuberculosis not present.....	Moro	1	29
	von Pirquet	7	23
Suspected pulmonary tuberculosis.....	Moro	14	14
	von Pirquet	24	4
Arrested pulmonary tuberculosis.....	Moro	5	2
	von Pirquet	5	2
Early and slight pulmonary tuberculosis.....	Moro	40	11
	von Pirquet	45	6
Advanced pulmonary tuberculosis.....	Moro	14	7
	von Pirquet	17	4
Lymph node tuberculosis .....	Moro	7	0
	von Pirquet	7	0
Suspected but non-tuberculous lymph nodes.....	Moro	0	2
	von Pirquet	0	2
Testicular tuberculosis .....	Moro	2	1
	von Pirquet	2	1
Bone tuberculosis .....	Moro	16	3
	von Pirquet	15	4
Pulmonary tuberculosis with fever.....	Moro	0	3
	von Pirquet	3	0

## GROUP OF SUSPECTED PULMONARY TUBERCULOSIS (TWENTY-EIGHT CASES)

The suspicion of tuberculosis in some of these cases was based on a history with or without signs and in others on physical signs alone. In 14 cases the Moro reaction was positive and in 24 the von Pirquet. Although we have not been able to follow out all the cases, we have acquired the impression that a suspicion of tuberculosis is greatly strengthened by the positive outcome of these tests, particularly of the Moro. A careful study of suspected cases in which the patients have reacted to the inunction will often reveal evidence on which a positive diagnosis can be based. For example, in one case of suspected pulmonary disease, the patient subsequently developed hemoptysis, râles at one apex and a sharp fibrinous pleurisy.

## GROUP OF ARRESTED PULMONARY TUBERCULOSIS (SEVEN CASES)

In 7 arrested cases there were 5 positive results to each test. One patient showed a positive Moro and a negative von Pirquet, while another presented the reactions reversed.

## GROUP OF EARLY AND SLIGHT PULMONARY TUBERCULOSIS (FIFTY-ONE CASES)

In 51 cases the Moro reaction was positive in 40, the von Pirquet in 45.

## GROUP OF ADVANCED PULMONARY TUBERCULOSIS (TWENTY-ONE CASES)

Out of 21 cases the Moro was positive in 14 and the von Pirquet in 17. The general belief seems to be that in advanced tuberculosis the various reactions to tuberculin are more frequently negative than in the earlier stages of the disease. In our cases the Moro reaction was positive in advanced pulmonary tuberculosis in  $66\frac{2}{3}$  per cent., about 12 per cent. less frequently than in early tuberculosis (78 per cent.).

It must be taken into account, however, that the number of advanced cases was less than half the number of the early. If a similar number of advanced and early cases had been examined it is not unlikely that the percentage of positive reactions in the former would have been smaller.

## GROUP OF LYMPH NODE TUBERCULOSIS (SEVEN CASES)

Seven cases were available for examination. In 2 other cases in which lymphatic tuberculosis was suspected the reactions were negative. In one patient it subsequently transpired that the adenitis was due to a carious tooth; in the other, to pediculosis capitis. In both instances the glandular swelling disappeared after appropriate treatment. In one case glands of the neck which were clearly tuberculous slowly diminished in size after the reactions occurred, and tests applied two months after the first gave very much less marked reactions. These facts are cited, not as evidence of the therapeutic value of tuberculin salve, but simply for what they are worth. In this connection Moro's observation, that a case of lupus improved greatly under treatment with tuberculin salve, is interesting.

## GROUP OF TESTICULAR TUBERCULOSIS (THREE CASES)

In 3 cases, 2 patients were positive to both tests. Of the positive cases, 1 was clearly tuberculosis, the other, on section after operation, proved to be sarcoma. The third case was probably one of sarcoma.

## GROUP OF BONE TUBERCULOSIS (NINETEEN CASES)

In 19 cases, the Moro reaction was positive 16 times, the von Pirquet 15. In one patient with advanced caries of the spine and tubercle bacilli in the sputum, there was not the slightest evidence of a reaction of any kind.

## GROUP OF CASES WITH FEVER (THREE)

An opportunity was offered at the Hudson Street Hospital to apply the reactions in three cases characterized by continuous fever. In an early case, the patient was thought, on admission, to be suffering from

typhoid fever. A few râles were subsequently found at one apex and tubercle bacilli demonstrated in the sputum on more than one occasion. The second case was clinically a subacute miliary tuberculosis in an alcoholic, with fatal termination. There never was any sputum obtainable and an autopsy was not granted, but the development of the physical signs and the clinical picture were so similar to those of the frequent proved cases observed at the hospital that there can be little doubt of the diagnosis. The patient had an alcoholic neuritis with paralysis of the diaphragm which proved an absolute hindrance to the expulsion of sputum. The third case was one of pneumonic phthisis; after several examinations tubercle bacilli were repeatedly demonstrated. In all these cases the Moro reaction was negative, the von Pirquet positive.

#### CASES WITH PREVIOUS CONJUNCTIVAL TESTS

In 9 of the cases, a conjunctival test had been made, at least two months before the skin reaction in every instance. In two advanced cases negative conjunctival results, but good skin reactions were obtained. Seven of the patients had given positive eye results. Three of these cases were advanced, and all the patients gave positive von Pirquet reactions, but only 2 were positive to the Moro. Three were early cases, 2 of the patients reacting to both tests and 1 reacting to neither. The seventh patient about whom a suspicion of tuberculosis was entertained was negative to both skin reactions.

#### MORO REACTION ALONE POSITIVE

The Moro reaction occurred alone in only 4 cases, in an early pulmonary, in a suspected pulmonary, in an arrested pulmonary and in a bone case.

#### RESULTS OF OTHER OBSERVERS

Heinemann,<sup>2</sup> in using Moro's salve, tested 66 patients who three weeks previously had been subjected to the conjunctival reaction. Forty-three of these patients gave positive salve reactions, while but 34 had reacted to the eye test. He says that at first sight one would believe the Moro more sensitive than the Calmette, but he thinks the previous eye reactions were to some extent responsible for the hypersensitiveness to the salve.

In 108 cases, Heinemann got 41 positive reactions. In 66 cases he made control experiments with 10 per cent. chrysarobin ointment. In 6 patients, 3 positive and 3 negative to the Moro test, he observed a dermatitis at the site of the control inunction, which, however, ran its course under an entirely different picture. Heinemann says that in non-sus-

pects the conjunctival reaction is positive in 16 per cent., the Moro in 17 per cent. of the cases. It is interesting to note that of his 12 non-suspects to react, 7 were patients with chronic nervous diseases. He regards the salve as possessing a practical advantage over the conjunctival reagent.

The work of Fehsenfeld,<sup>5</sup> who has reported 3 cases in which the patients gave positive ocular reactions during life and showed no evidence of tuberculosis on autopsy, is valuable in proving hypersensitiveness to tuberculin without tuberculosis. One of these patients had myelitis.

In a series of 241 adult cases, Emmerich<sup>4</sup> used the Moro reaction. In 121 of these, the von Pirquet reaction was also used. In manifest tuberculosis of all stages, the Moro reaction was positive in 15 out of 31 cases, the von Pirquet in 19. In 30 suspicious cases the Moro was positive in 25, the von Pirquet in 29. In 60 non-suspicious cases the salve reaction was positive in 19, the von Pirquet in 44 cases. In a series of 120 cases, in which the salve was the only tuberculin test used, the reaction was positive in 9 out of 15 tuberculous cases; it was positive in 15 out of 21 suspicious cases and in 28 out of 84 non-suspicious cases. He concludes:

1. The inunction reaction gives fewer positive results than the von Pirquet in patients clinically free of tuberculosis.
2. It is easier to carry out than the cutaneous reaction and is absolutely harmless.
3. In progressive tuberculosis it "misses fire" earlier than the von Pirquet.
4. Since latent foci react to it, it is to be regarded of diagnostic importance only in a limited degree.

Webb<sup>6</sup> has reported 155 Moro reactions, with positive results in 69 cases. In 85 apparently normal persons, 19 reactions were positive; 14 of these patients were subsequently found to be tuberculous by other diagnostic methods. Two of those who did not react were afterward proved tuberculous. In 15 well-marked cases, 7 gave negative, 8 positive results. In 39 suspected cases, 31 were positive. In 12 clinically early cases, only 1 was negative. In 5 suspected cases, the conjunctival test was made simultaneously. In 3 positive Moro tests the conjunctival reaction was positive, in 2 negative. In 1 case the conjunctival was positive, the Moro negative. He believes in skin reactions, especially the Moro, but very properly insists on the importance of their careful interpretation. Hamill, Carpenter and Cope,<sup>7</sup> in an important contribution, analyze their results in 158 conjunctival reactions, 159 von Pirquet reac-

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6. Webb (Gerald B.): The integumental tuberculin reactions, with report of 155 Moro inunction reactions. *Jour. Am. Med. Assn.*, 1908, li, 1271.

7. Hamill (S. McC.), Carpenter (H. C.) and Cope (T. A.): A comparison of the von Pirquet, Calmette and Moro tuberculin tests and their diagnostic value. *THE ARCHIVES INT. MED.*, 1908, ii, 405.

tions and 154 Moro reactions. The subcutaneous test was used in 85 of these cases, "in confirmation of the others." Children in the St. Vincent's Home, Philadelphia, were examined, and a smaller group outside that institution. Taken together there were 110 clinically non-tuberculous, of which 58.2 per cent. reacted to some of the various reactions, 50 per cent. to the Moro reactions, and 49 per cent. to the von Pirquet. Of 28 suspected cases, 82.1 per cent. reacted to the various tests, 78.5 per cent. to the Moro, 82.1 per cent. to the von Pirquet. Of 22 tuberculous cases, 95.4 per cent. reacted to the various tests. In only 18 of these cases was the Moro done, and it was positive in 77.7 per cent., while in 19 cases the von Pirquet was positive in 84.2 per cent. The paper is very exhaustive and presents excellent illustrations in color of the eye and skin reactions. The results in this work of the Moro and von Pirquet reactions are nearly alike, but it must be remembered that Hamill and his collaborators were working with children, while the other reports mentioned dealt with adults or adults and children.

#### INTERPRETATION

The important thing to bear in mind concerning the salve reaction is that not every individual that shows it is tuberculous and that not every tuberculous patient reacts. Its true value can be appreciated only when it is interpreted in connection with a past or present history of tuberculous disease and in connection with physical signs. A patient may give a marked reaction and yet the character of the physical signs and the patient's history may be such as to point conclusively to a healed process. Again, the patient's history, even in the absence of physical signs, with a positive reaction, often lead to a diagnosis of active tuberculosis. In general, when a reaction occurs the physician must determine: first, whether the hypersensitiveness is due to tuberculosis; second, whether, if due to tuberculosis, the disease is cured or active. The reaction helps out other clinical means of investigation, but will never replace them.

#### CONCLUSIONS

1. The Moro test is absolutely harmless and simple to use.
2. It is better adapted to use among adults than the von Pirquet test, because it does not produce a reaction so frequently among those clinically free from tuberculosis.
3. It produces a reaction probably about as frequently as the ocular reaction in the tuberculous and in the clinically free cases, but is devoid of the danger incident to the conjunctival test.

# THE CUTANEOUS AND CONJUNCTIVAL TUBERCULIN TESTS IN THE DIAGNOSIS OF PULMONARY TUBERCULOSIS

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## INTRODUCTION

So much has been written about the cutaneous and conjunctival tuberculin tests that one feels constrained to offer an apology before making a further contribution. As the value of the tests is still under judgment and as questions of technic remain unsettled, however, we beg to be borne with for adding our word to the discussion. What we have to say is the result of over a year of experience with patients coming to the Phipps Dispensary of the Johns Hopkins Hospital. It is important that these tuberculin tests should be tried on as varied a material as possible, and we feel that we have had not only a rich material at our disposal, but one differing in many ways from the cases described in most of the reports that have appeared. All the patients that are sent us are, it is true, suspected more or less gravely of having tuberculosis, and in nearly all instances of having pulmonary tuberculosis. One of the main functions of the dispensary is to diagnose and differentiate this material, and after prolonged observation we find that somewhat less than two-thirds of our patients turn out to have definite tuberculous disease. The group of doubtful and non-tuberculous patients is becoming larger and larger as the work of the dispensary extends. We receive patients who come to us with a diagnosis of pulmonary tuberculosis already made. Many others have pulmonary symptoms and are sent to us for diagnosis, and in a certain proportion of this group it turns out that the pulmonary symptoms are due to disease other than tuberculosis. We further make a special effort to examine as many members as possible of the families of advanced tuberculous patients, and, lastly, a large number of cases are sent for examination by the tuberculosis nurses and the agents of the Charity Organization Society. In the last group many, perhaps even the larger portion, are apparently well and are sent to us merely to exclude the presence of tuberculosis or to get a clean bill of health so that they may be admitted to various institutions that aim to exclude infectious diseases. Our clientele, then, consists of

healthy individuals, of persons suspected of having tuberculosis, and of the definitely tuberculous. It is important, but perhaps not necessary, to emphasize that all of our patients are from the lower walks of life and many from below the poverty line, and, after all, most of them come to us because they do not feel well or because those who are watching over them see in their surroundings those conditions which lead them to fear that they already have or else are in position to develop manifest tuberculous disease.

For the past year it has been our practice to perform, in a routine manner, the skin and conjunctival tuberculin tests on as many of the patients as has been practicable. It has seemed to us that much of the confusion and lack of agreement as to the value of these tests is referable to imperfect classification. It is not enough to say so many healthy individuals react and so many tuberculous do not, but we wish to know under what conditions healthy individuals react and under what circumstances the tuberculous do not. For this reason we have gone rather into detail with our cases and figures, perhaps into more detail than the importance of the subject demands; but we have tried to include in our tables everything of interest so that the basis for our deductions may be readily scanned. The number of our cases is not very large, so our results are significant rather than conclusive; but we believe that they are of more value than an equal number collected from various sources, because they have been uniformly observed. All of the questionable cases and many of the others have been examined by either one or the other of us. We mention this not to suggest that we are more skilful in diagnosis than others, but as a mark that the work was carefully controlled and judged by a standard which is, at least, uniform.

For the purpose of classification we have divided our material into six groups as follows:

*Group 1. Non-tuberculous Cases. Total Number 64.*—This group includes all of those patients who had absolutely no symptoms or signs of any tuberculous disease and those with pulmonary symptoms in whom these symptoms were manifestly due to some disease other than tuberculosis. The cases are classed as follows:

Negative history and examination.....	37 cases
Chronic endocarditis .....	4 cases
Bronchitis and emphysema.....	3 cases
Bronchitis .....	3 cases
Bronchial asthma .....	3 cases
Enlarged tonsils and adenoids.....	3 cases
Chronic pharyngitis .....	2 cases
Lobar pneumonia .....	2 cases
Empyema following pneumonia.....	2 cases

Secondary anemia .....	1 case
Chronic gonorrhea .....	1 case
Tertiary syphilis .....	1 case
Neurasthenia .....	1 case
Aneurism of arch of aorta.....	1 case

*Group 2. Doubtful Cases. Total Number 191.*—This group includes all those patients who have any symptoms or any physical signs that might be referred to tuberculosis and for which no perfectly satisfactory explanation can be given. The fact, however, that they have come to us with symptoms, though in themselves often slight, and frequently with a history of more or less intimate exposure, has led us to regard them with suspicion. Usually repeated examination has failed in any way to confirm these suspicions. The group comprises such cases as that of the wife of a tuberculous patient who herself has a little cough but no physical signs: a person who is unaccountably run down and in whose family there is a case of tuberculosis; children of the tuberculous who are thin and generally below par, or patients with a few symptoms and indefinite physical signs at an apex.

*Group 3. Probable Cases. Total Number 75.*—This group was especially made to free our incipient class as far as possible from the personal equation. It must be granted that the diagnosis of incipient pulmonary tuberculosis has a large individual factor, depending, in great measure, on the skill and training of the diagnostician. We feel confident that at least 75 per cent. of the cases in the probable group would be classed by men skilled in the diagnosis of pulmonary tuberculosis as incipient cases. The symptoms and signs, however, are not definite enough to permit this conclusion with certainty. Twenty-two of the patients received subcutaneous injections of tuberculin, and all but one gave febrile and constitutional reactions. Six of these 22 gave suggestive signs of even a focal reaction. The patient in the one negative case had such definite symptoms and signs of early pulmonary tuberculosis that the case was retained in spite of no reaction to 10 mg.

*Group 4. Incipient Cases. Total Number 28.*—This number is so small, because our list has been depleted by transfers to the probable group. We feel that there can be no question about the diagnosis in a single one of these cases. Eleven of the 28 had tubercle bacilli in their sputum, 6 more gave a definite focal reaction to subcutaneous injections of tuberculin, and in the remaining 11 cases the symptoms and physical signs were so definite as to leave little, if any, doubt about the correctness of the diagnosis.

*Group 5. Moderately Advanced Cases. Total Number 91.*—Forty-seven of these patients had tubercle bacilli in their sputum; the others



were diagnosed from the history and the evident physical signs. No questionable cases are included.

*Group 6. Far Advanced Cases. Total Number 82.*—In all these patients the diagnosis was evident from the history and physical signs. Thirty-one of the 82 had tubercle bacilli in the sputum.

We wish to emphasize the care we have taken in distributing our cases according to this classification. After grouping our material we went over it again to make it certain that no questionable cases were included with the tuberculous. We can not say with certainty that no errors have occurred, but those that may be present are due to the inherent difficulty of making a satisfactory clinical classification.

#### THE CUTANEOUS REACTION

During the summer and fall following von Pirquet's<sup>1</sup> announcement of a new method of diagnosing tuberculous infections in children we made a number of observations which have been previously published.<sup>2</sup> Our procedure was to apply a drop of pure tuberculin to the skin and to make through it with the point of a scalpel a few very superficial incisions. As controls, incisions were made in the bare skin and also through a drop of 50 per cent. glycerin. As we never observed any reactions in the controls, they were later abandoned. Our results plainly indicated that so large a percentage of apparently healthy adults were reacting that the test would prove of diagnostic value only if it were negative. To make it less delicate we resorted to dilutions of tuberculin. In the series we are at present reporting, all of the tests were made as follows: On the cleaned outer surface of the arm were placed in a row a drop of a 1 per cent. solution, a drop of a 5 per cent. solution and a drop of a 20 per cent. solution of old tuberculin.<sup>3</sup> With a sterilized scalpel two small parallel incisions were made into the skin, first through the 1 per cent., then through the 5 per cent., then through the 20 per cent. solution. It was aimed to make the incisions so superficial that there would be no bleeding, but frequently a few small drops of blood appear along the line of incision. This seems in no way to interfere with the delicacy of the test. In the beginning we allowed the tuberculin to remain on the arm two or three minutes after the incisions were made, then covered it with a small piece of gauze held in place by straps of

1. Von Pirquet: Berl. klin. Wehnschr., 1907, xliv, 699.

2. Hamman: Use and value of tuberculin in the diagnosis of pulmonary tuberculosis. THE ARCHIVES INT. MED., 1908, i, 443.

3. The tuberculin used in these experiments was obtained from the Alexander Serum Co. Unless otherwise specified tuberculin from cultures of the human type was employed.

adhesive plaster. In this way the tuberculin is kept a longer time in contact with the skin. More recently we have allowed the drops to remain for at least five minutes after incision before covering them with gauze. This difference in the length of exposure has made absolutely no change in our results and is, we think, of quite secondary importance.

The only technical difference between this method of performing the cutaneous test and that used by some others is in the manner of causing the abrasion. Von Pirquet employs an instrument with a spatula-shaped platinum point and a heavy base which is rotated three or four times through the drop of tuberculin, causing a pit-like abrasion of the skin. Von Pirquet was kind enough to send us one of his instruments, and for some weeks we carried on, side by side, tests made with it and with a scalpel. We finally returned to the incision method as our routine. The objections to von Pirquet's instrument are that it causes a good deal of pain, which is an important consideration in children, and that the reading of the results is more difficult. The control pit is always surrounded by an inflammatory areola which is hard to distinguish from a mild reaction, and the reactions on the whole are milder and less definite. It has been common to see no or slight reactions to the von Pirquet method, while those to the incision were positive. It requires some technical skill, too, to apply just the right amount of pressure to the instrument. Perhaps some of the negative cases referred to might have been positive if more pressure had been made. The incision method is painless, the control shows absolutely no reaction and there can be no variation in the manner of application.

The result of these tests we have classified under five headings:

1. Negative Reactions.—No redness or infiltration about the incisions.
2. Slight Reactions.—Definite redness and some infiltration about the incisions.
3. +Reaction.—Rather wide area of redness which is definitely raised.
4. ++Reaction.—Wider area of redness and more marked elevation than +.
5. +++Reaction.—Unusual redness and a wide area of infiltration.

As our material consists entirely of dispensary patients, the reading of the reaction is made after from twenty to twenty-four hours, and frequently again after forty-eight hours. The results recorded in our tables

are all the twenty-four readings. Wolff-Eisner<sup>4</sup> has divided skin reactions into three groups:

Type 1.—The active reaction, the specific normal reaction of the tuberculous. It begins from four to six hours after inoculation and attains its maximum in from twenty to twenty-four hours. The maximum stage persists during the second day and shows a decrease on the third or at latest on the fourth day.

Type 2.—The premature reaction, characterized by a rapid course and a slight intensity. It begins in about six hours, reaches its maximum speedily, sometimes after only ten hours, and disappears rapidly, at the latest on the second day. This type is supposed to occur in patients with manifest tuberculosis who are not doing well.

Type 3.—The late and persisting reaction. It begins like the others, but reaches its maximum slowly and gradually, usually at the end of the second day and in some cases still later, the maximum persisting unchanged usually for a week. This type is supposed to occur in patients with an inactive tuberculous lesion.

He adds that these types bear no relation to the concentration of the tuberculin.

We have no experience with premature reactions, for our patients come for inspection only after twenty-four hours. About delayed and persisting reactions, too, we have little to say. Only five cases were observed giving definite delayed reactions, and all 5 were among the non-tuberculous cases.

Unusually severe reactions we have found rather uncommon.

Well-marked vesiculation occurred in but 5 of our 526 cases. One case went on to definite pustulation.

#### THE CONJUNCTIVAL REACTION

In a discussion of von Pirquet's paper on the cutaneous reaction to tuberculin, Wolff-Eisner announced that tuberculin instilled into the conjunctival sac would likewise cause a local reaction in tuberculous individuals. Calmette<sup>5</sup> only a few weeks later published the results of similar tests that he had made apparently independently. Wolff-Eisner used a 5 per cent. solution of old tuberculin and continues to use various dilutions of old tuberculin, as do most German clinicians. Calmette precipitates old tuberculin with alcohol and, after washing the sediment, redissolves it in salt solution in from 0.5 to 2 per cent. strengths. It

4. Wolff-Eisner: *Die Ophthalm- und Kutan- Diagnose der Tuberkulose*. Beitr. z. klin. d. Tuberk., 1908, ix, 1.

5. Calmette: *Presse méd.*, 1907, xv, 388.

has been pointed out and deserves to be emphasized that these solutions of purified tuberculin are approximately ten times stronger than those of old tuberculin, so that a 1 per cent. solution of the former is about equal to a 10 per cent. solution of the latter. This is a matter of much importance in comparing the results of various observers. In the present series of cases our method has been this: After carefully inspecting the eyes to see that the conjunctivæ are healthy and alike in appearance, one drop of the 1 per cent. solution of old tuberculin is instilled into the left conjunctival sac. The sac is then manipulated so that the fluid is equally distributed. The following morning, after twenty to twenty-four hours, the patient comes for inspection, and if the left eye shows no reaction a drop of a 5 per cent. solution is instilled into the right conjunctival sac. At the end of another twenty to twenty-four hours the eyes are again inspected, and in some instances a third instillation, consisting of a drop of 1 per cent. old tuberculin, was made in the left eye. In some of the early cases a 2 per cent., instead of a 5 per cent., solution was used for the second instillation. These particulars are indicated in the tables that follow. As in the skin test, all of the readings were made after twenty to twenty-four hours.

The following grouping of the reactions was adopted:

Negative.—No discernible difference in the two conjunctivæ.

Slight or doubtful.—Conjunctiva of the eye receiving the injection a little redder than the other eye, but the difference not marked enough to permit the reaction to be called definitely positive. In most instances the redness and injection are limited to the caruncle.

+.—Definite palpebral redness.

++.—More marked palpebral redness with secretion.

+++.—Palpebral and bulbar redness with subjective symptoms and well-marked secretion.

In making the readings the lower lids are well pulled down and the patient directed to move the eyes in different planes. In making up our tables from the records we have omitted the group "slight or doubtful" and placed all of these cases in the negative group. We found that so frequently the note was made "slight" reaction to the 1 per cent. instillation followed by "negative" to the 5 per cent. that we were convinced that retaining this class was a useless refinement. It will be appreciated that a slight or doubtful reaction to a conjunctival test is quite different from a slight reaction to the cutaneous test. The latter is always definitely positive as compared with a control, and we have counted it a positive reaction in our tables, giving summaries.

## THE RESULTS OBTAINED

Table 1 shows the results of the application of the tests in the non-tuberculous cases. It is seen at a glance how very infrequent a conjunctival reaction is and how very common the skin reactions are, particularly to the 20 per cent. tuberculin. Both of the patients reacting to the first 1 per cent. eye instillation give a history of marked exposure to the disease.

Patient 2670, negative to 1 per cent., but positive to the instillation of 5 per cent., also gives a definite history of exposure to the disease.

TABLE 1.—CUTANEOUS AND CONJUNCTIVAL TUBERCULIN REACTIONS IN 63 NON-TUBERCULOUS CASES.

Strength of Tuberculin.	No. of Skin Reactions.			No. of Conjunctival Reactions.			
				Instillation.			
				1st.	2d.		3d.
	1%	5%	20%	1%	2%	5%	1%
Negative reaction.	53	31	17	61	9	32	6
Slight reaction.	2	4	8				
+	6	20	17	2	0	0	2
++	2	7	18	0	0	1	0
+++	0	1	3	0	0	0	0

There are, however, 21 more patients that gave a history of marked exposure in the family. None of these reacted to the first instillation of 1 per cent., and three failed to react to an instillation of 2 per cent. and 11 to 5 per cent. in the opposite conjunctival sac, and 1 even to the second instillation of 1 per cent. in the first conjunctiva.

One patient, a boy, aged 12, with asthma, showed a delayed skin reaction which came on after forty-eight hours. The 1 and 5 per cent. conjunctival tests were negative.

Table 2 gives the results in the doubtful cases. Four of the patients did not receive the 1 per cent. tuberculin on the skin and 2 have no record of the 1 per cent. eye instillation. One of these failed to return to have the 1 per cent. instillation inspected, and subsequently the instillation of 5 per cent. was negative; the other received only one instillation, and that of 5 per cent., which was negative.

In this table, too, the much higher percentage of reactions to the skin test is seen.

Besides the 14 patients receiving a second instillation of 1 per cent. in the same eye, one received a second instillation of 5 per cent. and gave a +++ reaction, and two a second instillation of 2 per cent., both remaining negative. Four of the patients showed delayed skin reactions and one a delayed conjunctival reaction to 5 per cent.

TABLE 2.—CUTANEOUS AND CONJUNCTIVAL REACTIONS IN 191 DOUBTFUL TUBERCULOUS CASES.

Strength of Tuberculin.	No. of Skin Reactions.			No. of Conjunctival Reactions.			
				Instillation.			
				1st.	2d.		3d.
	1%	5%	20%	1%	2%	5%	1%
Negative reaction.	120	67	35	165	24	83	9
Slight.	23	20	20				
+	36	73	55	13	4	11	2
++	7	25	55	8	2	4	2
+++	1	6	26	3	0	0	1
Test not given.	4			2			

Three of the patients showed an unusual reaction. They received an instillation of 1 per cent., which the following day was negative, and a drop of 5 per cent. was then instilled into the opposite conjunctiva. On the day after, although the 5 per cent. was negative, the 1 per cent. showed a mild positive reaction. We can suggest only one of two explanations: first, that these were delayed reactions, which seems improbable, and, second, that the first conjunctiva had become so sensitized by the 1 per cent. tuberculin that it reacted to even the small amount that reached it from the instillation of the 5 per cent. in the opposite conjunctival sac. How it reached the first eye it is difficult to say. There are no definite channels of lymphatic connection between the two conjunctivæ. It is hardly probable that a large enough amount could have been absorbed to cause a reaction in the first eye by reaching it through the general circulation. It is possible that the patients, in rubbing the eyes, carried some of the tuberculin from the inoculated conjunctiva to the other. If Moro's<sup>6</sup> views are correct, these reactions might be due to a reflex nervous influence.

6. Moro: Tuberkulinreaktion und Nervensystem. München. med. Wchnschr., 1908, lv, 2025.

In one instance a ++ reaction to the 1 per cent. instillation was followed by phlyctenular conjunctivitis. The eye was still red, but the inflammation was rapidly subsiding at the end of two weeks. In the doubtful group, 51 patients gave a history of prolonged exposure in the family.

Eight, or 15.7 per cent. were positive to 1 per cent. instillation.

Forty-three, or 84.3 per cent., were negative to a 1 per cent. instillation.

Seven of the negative cases were negative to a second instillation of 2 per cent. and 23 to a second instillation of 5 per cent.

Two of the negative cases became positive to a second instillation of 2 per cent. and one positive to a second instillation of 5 per cent.

This is a very little higher percentage than for the whole group and would indicate that exposure to tuberculosis without signs or symptoms of disease plays no great part in the production of the conjunctival reaction.

Table 3 gives the results in the probable cases. The increasing number of both eye and skin reactions is seen.

TABLE 3.—CUTANEOUS AND CONJUNCTIVAL TUBERCULIN REACTIONS IN 71 PROBABLY TUBERCULOUS CASES.

Strength of Tuberculin.	No. of Skin Reactions.			No. of Conjunctival Reactions.			
				Instillation.			
				1st.	2d.		3d.
	1%	5%	20%	1%	2%	5%	1%
Negative reaction.	32	10	4	49	6	18	4
Slight.	9	4	2				
+	26	32	17	10	3	8	1
++	2	22	28	10	2	5	2
+++	0	3	20	2	0	1	2
Test not given.	2						

Under the ++ reaction to the first instillation of 1 per cent. are included two cases in which the reaction became positive only after the instillation of 5 per cent. in the opposite eye. These are similar to the three cases referred to in the doubtful group, only here the reaction was very marked and both the 1 per cent. and 5 per cent. were positive. In one of the cases the 1 per cent. and 5 per cent. reactions were about equally severe—both ++ reactions; in the other the 1 per cent. was even more severe than the 5 per cent., a ++ and a + reaction, re-

spectively. This certainly indicates a sensitizing action of the first instillation rather than a delayed reaction.

Sixteen of the patients gave a history of marked exposure to tuberculosis in the family or in the workshop.

Three of the 16, or 19 per cent., reacted to the first conjunctival instillation of 1 per cent. In 4 of the negative cases the patients received an instillation of 2 per cent. in the other conjunctiva, 2 reacting and 1 negative; 8 an instillation of 5 per cent., 3 reacting and 5 negative; 2 a second instillation of 1 per cent. in the first conjunctiva, 1 reacting and 1 negative.

Table 4 gives the results in the incipient cases. In one case the skin test and the 1 per cent. conjunctival test were omitted, but an instillation of 2 per cent. was positive.

TABLE 4.—CUTANEOUS AND TUBERCULIN REACTIONS IN 28 INCIPIENT CASES.

Strength of Tuberculin.	No. of Skin Reactions.			No. of Conjunctival Reactions.			
				Instillation.			
				1st.	2d.		3d.
	1%	5%	20%	1%	2%	5%	1%
Negative reaction.	12	6	3	14	4	8	1
Slight.	2	3	1				
+	9	6	5	6	0	1	
++	4	7	8	2	1		
+++	0	5	10	5	0		
Test not given.	1	1	1	1			

One patient had apparently an old fibroid lesion. The skin test showed a + reaction to 1 per cent., a + to 5 per cent. and a ++ to 20 per cent. Both the 1 per cent. and the 5 per cent. conjunctival instillations were negative.

Another patient in an apparently fibroid case gave 0, 0 and + skin reactions and was negative to both the 1 per cent. and 5 per cent. conjunctival instillations.

Table 5 gives the results in the moderately advanced cases.

Two patients failed to return for an inspection of the 1 per cent. conjunctival instillation. Both subsequently gave a ++ reaction to 5 per cent.



Two patients showed vesiculation of the 5 per cent. and 20 per cent. cutaneous reactions and one patient pustulation.

One patient gave a violent conjunctival reaction to 1 per cent. with profuse purulent discharge.

TABLE 5.—CUTANEOUS AND CONJUNCTIVAL TUBERCULIN REACTIONS IN 91 MODERATELY ADVANCED CASES.

Strength of Tuberculin.	No. of Skin Reactions.			No. of Conjunctival Reactions.			
				Instillation.			3d.
	1%	5%	20%	1st.	2d.	3d.	
	1%	5%	20%	1%	2%	5%	1%
Negative reaction.	36	6	3	26	1	7	
Slight.	8	7	6				
+	41	43	19	27	....	5	
++	6	29	36	20	...	7	
+++	0	6	27	16			
Test not given.	....	....	...	2			

TABLE 6.—CUTANEOUS AND CONJUNCTIVAL TUBERCULIN REACTIONS IN 82 FAR ADVANCED CASES.

Strength of Tuberculin.	No of Skin Reactions.			No. of Conjunctival Reactions.			
				Instillation.			3d.
	1%	5%	20%	1st.	2d.	3d.	
	1%	5%	20%	1%	2%	5%	1%
Negative reaction.	44	20	7	25	3	5	
Slight.	6	6	8				
+	27	25	21	22	..	6	1
++	5	26	21	25	....	1	
+++	0	5	25	9			
Test not given.	...	...	....	1			

Three of the patients had old apparently fibroid lesions.

One gave a + conjunctival reaction to 1 per cent.; one was negative to 1 per cent. and gave a + reaction to 5 per cent.; one was negative to 1 per cent. and received no further instillations. All three gave definite cutaneous reactions.

Table 6 gives the results in the far-advanced cases. One patient failed to return for inspection after the 1 per cent. eye instillation. The subsequent 5 per cent. instillation gave a + reaction.

One patient gave a +++ conjunctival reaction to 1 per cent. with purulent secretion.

## GENERAL SUMMARY OF THE RESULTS

Table 7 shows at a glance the summary of the results. To the 1 per cent. conjunctival instillation 3 per cent. of the non-tuberculous cases react, 13 per cent. of the doubtful, 31 per cent. of the probable, 48 per cent. of the incipient, 71 per cent. of the moderately advanced and 69 per cent. of the far advanced. The percentage of the reactions to the 5 per cent. instillation raises the proportion still higher. The method of arriving at this proportion is as follows: Allow, as an example,

TABLE 7.—TABLES 1 TO 6 CONDENSED AND STATED IN PERCENTAGES.

Strength of Tuberculin.	Per Cent. of Skin Reactions.												Per Cent. of Conjunctival Reactions.					
	1%				5%				20%				1%				5%	
Degree of Reaction.	0	+	++	+++	0	+	++	+++	0	+	++	+++	0	+	++	+++	0	Pos.
Non-tuberculous cases.....	81	13	3	0	49	38	11	2	27	40	29	5	97	3	0	0	94	6
Doubtfully tuberculous cases.....	64	32	4	0.5	35	49	13	3	18	39	29	13	87	7	5	2	75	25
Probably tuberculous cases.....	46	51	3	0	14	51	31	4	6	26	40	28	69	14	14	3	39	61
Incipient tuberculous cases.....	44	41	15	0	22	35	26	9	11	22	30	36	52	22	7	19	48	52
Moderately advanced tuberculous cases...	40	54	6	0	7	55	32	6	3	27	40	30	29	30	23	17	13	87
Far advanced tuberculous cases.....	54	40	6	0	24	38	32	6	9	35	26	30	31	27	31	11	14	86

that 300 patients receive the 1 per cent. instillation and of this number 100 react, of the 200 negative cases only 100 return for the 5 per cent. instillation, and of this number 50 react. It is approximately safe to assume that if 50 of the 100 patients that returned reacted, 50 of the other 100 patients that did not return would also have reacted, making a total of 100 reactions to the 5 per cent. among the 200 that did not react to the 1 per cent. It is further certain that the 100 patients reacting to the 1 per cent. would have reacted to the 5 per cent. had this test been given, which makes a total of 200 reactions to the 5 per cent. out of the 300 cases, or 67 per cent. Calculated in this manner, the 5 per cent. instillations give 6 per cent. of reactions in the non-tuberculous group, 25 per cent. in the doubtful, 61 per cent. in the probable, 52 per cent. in the incipient, 87 per cent. in the moderately ad-

vanced, and 86 per cent. in the far advanced. Under the skin reactions one easily follows the percentages. In the moderately advanced group there are 40 per cent. negative reactions to the 1 per cent., only 7 per cent. negative to the 5 per cent., and 3 per cent. negative to the 20 per cent. This is apparently a much more valuable diagnostic means in tuberculous cases than the conjunctival reaction, but unfortunately it loses in reliability when compared in the non-tuberculous and doubtful groups. In the non-tuberculous the negative reactions are only 27 per cent. and in the doubtful but 18 per cent.

TABLE 8.—CUTANEOUS AND CONJUNCTIVAL TUBERCULIN REACTIONS IN CASES IN WHICH TUBERCLE BACILLI APPEARED IN SPUTUM.  
INCIPIENT CASES, 11.

Strength of Tuberculin.	No. of Skin Reactions.			No. of Conjunctival Reactions.		
	1%	5%	20%	1%	2%	5%
Negative reaction.....	2	1	1	4	2	1
Slight.....	2	1	0			
+ .....	5	3	1	3		
++ .....	2	5	5	2		
+++ .....	0	1	4	2		
Test not given.....						

MODERATELY ADVANCED CASES, 47.

Negative reaction.....	22	1	1	9	1	1
Slight.....	3	4	2			
+ .....	17	25	10	13	....	3
++ .....	5	14	21	16	....	2
+++ .....	....	3	13	8		
Test not given .....	....	....	....	1		

FAR ADVANCED CASES, 31.

Negative reaction.....	15	7	2	6	2	1
Slight.....	3	5	5			
+ .....	10	7	7	10	....	1
++ .....	3	11	7	11	....	1
+++ .....		1	10	3		
Test not given .....	....	....	....	1		

We have constructed Table 8 of the cases in which there are tubercle bacilli in the sputum and Table 9 which may be directly compared with Table 7. We do not ourselves believe that Table 9 gives even as truthful

a statement as Table 7, for the number of cases is smaller and in the incipient group it is manifestly unjust to include only cases in which there are tubercle bacilli in the sputum. Knowing, as we think our tables plainly indicate, that patients with moderately advanced tuberculosis possess a greater conjunctival sensitiveness to tuberculin than early cases, one would expect that among patients in the incipient class those with tubercle bacilli in the sputum would give a larger percentage of reactions than those without tubercle bacilli. In the moderately and far advanced groups the percentage of reactions is also somewhat higher, but the difference is not greater than might be accidental. Under the skin reactions the figures correspond rather closely.

TABLE 9.—DATA OF TABLE 8 STATED IN FORM OF PERCENTAGES.

	Skin Reactions.												Conjunctival Reactions.					
	1%				5%				20%				1%				5%	
	0	+	++	+++	0	+	++	+++	0	+	++	+++	0	+	++	+++	0	+
Incipient cases.....	18	64	18	0	9	36	45	9	9	9	45	36	36	27	18	18	?	?
Moderately advanced cases.....	47	43	10	0	2	62	30	6	2	25	44	28	20	28	35	17	4	96
Far advanced cases.....	48	42	9	0	23	39	35	3	6	39	23	32	20	33	37	10	10	90

## THE RELATION BETWEEN THE SKIN AND CONJUNCTIVAL REACTIONS

It is of frequent occurrence to find that a patient giving no reaction to a conjunctival instillation will give a well-marked cutaneous reaction. The much larger number of skin reactions shows how common such a relation is. To explain this we may assume that certain cells in the body are more highly sensitized to tuberculin than other cells and that the skin possesses this hypersensitiveness to a much higher degree than the conjunctiva. This may be true and it seems not unreasonable, but we must consider, too, the differences in the method of application. No trauma is inflicted in making the conjunctival instillation and, although absorption from the sac is easy, this may, after all, be of fundamental importance. The relation of the intensity of the two reactions is by no means constant, there frequently being a marked skin reaction when the eye reaction is slight, and conversely, but by no means so commonly, a mild skin reaction when the conjunctival reaction is intense. Only rarely the eye reaction is positive when the skin is negative. These

relations are indicated in Table 10. It is impossible to offer any satisfactory reason why such variations should occur unless one would accuse the technic. While we think that this may at times be at fault, we do not believe that it is the source of all or even of many of these disagreements. From the table one sees that there is in general a correspondence between the two reactions. Nineteen per cent. of the 20 per cent. skin reactions are negative among those failing to react to the conjunctival instillation and no negatives to those giving a +++ conjunctival reaction, while the +++ skin reactions rise from 11 per cent. to 57 per cent.

TABLE 10.—RELATION BETWEEN THE CUTANEOUS AND CONJUNCTIVAL REACTIONS.

Conjunctival reactions to First Instillation of 1%.	Skin Reactions.																	
	1%						5%						20%					
	Neg.	Slight.	+	++	+++	Test not Given.	Neg.	Slight.	+	++	+++	Test not Given.	Neg.	Slight.	+	++	+++	Test not Given.
Negative... 342 cases...	231 68%	40 12%	58 17%	11 3%	0	2	122 35%	33 10%	133 39%	46 13%	8 2%	0	64 19%	37 11%	96 28%	107 31%	38 11%	0
+ ..... 80 cases...	31 40%	5 6%	38 47%	5 6%	0	1	13 16%	5 6%	30 37%	26 32%	6 7%	0	5 6%	4 5%	17 21%	27 24%	27 24%	0
++ ..... 63 cases...	28 44%	4 6%	25 40%	6 9%	0	0	6 9%	3 5%	26 41%	26 41%	2 3%	0	1 2%	4 6%	13 21%	21 33%	24 38%	0
+++ ..... 35 cases...	10 28%	0 0%	20 57%	4 11%	1 3%	0	1 3%	2 6%	5 14%	18 51%	9 26%	0	0 0%	1 3%	5 14%	9 26%	20 57%	0

Our main object in making the cutaneous test with different strengths of tuberculin was to see if we could find a particular dilution that would give results comparable to those from the conjunctival test or, indeed, results still more nearly in accord with the clinical findings. A glance at Tables 7 and 10 shows that the attempt is futile. Even to the 1 per cent. skin test 32 per hundred react among those negative to the conjunctival instillation, and to the 5 per cent. skin test 65 per hundred. On the other hand, 40 per cent. positive in the + degree to the conjunctival test are negative to the 1 per cent., and 16 per cent. to the 5 per cent. skin tests. In the 20 per cent. skin reactions nearly all the patients react, even those negative to the conjunctival test. Similarly, while the 20 per cent. skin test gives results more nearly in accord with the clinical diagnosis among the definitely tuberculous, it gives far too high readings among the non-tuberculous and doubtful. The 1 per cent. skin test, on the other hand, gives fair averages for the non-tuberculous and doubtful groups, but entirely too low readings for the defi-

nitely tuberculous. The 5 per cent. skin test stands between the two with too high percentages among the non-tuberculous and doubtful and too low among the definitely tuberculous. The results of the cutaneous and the conjunctival tests are by no means interchangeable and if each has a value both must be used.

#### THE RELATION BETWEEN THE SUBCUTANEOUS, THE SKIN AND THE CONJUNCTIVAL REACTIONS

The question of the relation between the skin and the conjunctival tests and the subcutaneous administration of tuberculin and the value of each method in diagnosis is, we feel, important enough to justify giving in detail the results of the three methods in 48 cases. Table 11 gives these results in a concise form which is readily scanned.

Of the 48 cases, the 4 non-tuberculous failed to react, although Patient 1827 had one temperature elevation of 100.6. This elevation followed one of the first injections and was not repeated after subsequent injections, and there were never any constitutional symptoms.

Of the 14 patients in the doubtful group, 8 gave definite febrile and constitutional reactions; 5 gave neither febrile reaction nor constitutional symptoms, and 1 had no constitutional symptoms, although the temperature went to 99.4.

Of the 21 patients in the probable group, 17 gave definite febrile elevations and constitutional symptoms. One patient reacted definitely, but the height of the temperature was not recorded. In two cases there was an elevation to but 99, with slight constitutional symptoms. One patient gave a definite focal reaction and two, suggestive signs of a focal reaction. One case was negative.

Of the 9 patients in the incipient group, all but one gave definite febrile and constitutional reactions. Seven gave definite focal reactions and one suggestive signs of a focal reaction. The negative case deserves special attention, as tubercle bacilli were reported in the sputum. The fact that a patient in an early stage of pulmonary tuberculosis with bacilli in the sputum should not react to even 10 mg. of tuberculin subcutaneously is such an unusual occurrence that one is immediately prompted to suggest the possibility of an error in the sputum report. This was our first thought and, as our positive slides are always saved, it was easy to verify the finding. The only possible source of error could, then, have been a faulty numbering of the slides, and, while careful inquiry fails to lend support to such view, its possibility has induced us to put an interrogation mark after the positive report. The

TABLE 11.—RELATION BETWEEN REACTIONS FROM CUTANEOUS, CONJUNCTIVAL AND SUBCUTANEOUS TUBERCULIN TESTS.

## NOT TUBERCULOUS

Disp. No.	Sex.	Age.	General Condition.	History and Examination.*	Sputum.	Subcutaneous Injections.							Skin Reaction †			Conjunctival Reaction.		
						Doses of Tuberculin.	Highest Temp.	Constitutional Reaction.	Local Reaction.	Focal Reaction.		Flare-up of Skin or Eye.	1%	5%	20+	1st.	Instillation.	
										Symptoms.	Signs.						1%	2%
1827	F.	19	Good...	F. h. neg.; no exposure; bronchitis and cough for 9 years; no definite physical signs.	None ..	1.5-1.2-1.5	100.6	0	+	0	0	0, 30 dys.	0	S.	S.	0	0	0
2587	F.	37	Fair...	F. h. neg.; no exposure; grip 4 mos. ago and since then pain in chest; slight dulness and suppressed b. s. at r. apex.	1 exam. 0	1.5-1.5	99.2	0	?	0	0	0, 2 mos..	0	+	+	0	0	0
3089	M.	36	Good...	F. h. neg.; no exposure; grip 15 mos. ago and cough since then; no definite physical signs.	1 exam. 0	1.5-1.2-6	99.2	0	Slight.	0	0	0, 13 dys.	0	+	++	0	0	0
3191	F.	14	Good...	S. has tb. and patient slept with her; cough, pain in chest and headache for 3 mos.; no definite physical signs.	No exam.	1.5-1.5-10	99.0	0	0	0	0	0, 20 dys.	0	0	0	0	0	0

## DOUBTFUL CASES

2691	F.	32	Good...	F. h. neg.; no exposure; cough and sticky feeling in throat since grip 4 mos. ago; enlarged thyroid; dulness and suppressed b. s. at r. apex; râles at l. apex.	None ..	1.5-1.5-10	99.8	0	+	0	0	0, 26 dys.	+	+	++	0	0	0
2683	F.	33	Good...	F. h. neg.; no exposure; sweats and weakness for 2 mos.; slight dulness and some loss of vesicular murmur at r. apex; few fine crackling râles.	None ..	1.5-1.3	?	++	++	0	0	0, 2 mos..	+	++	+++	0	0	0
2708	F.	17	Good...	F. h. neg.; no exposure; cough for 10 years; physical exam. negative.	4 exam. 0	1.5-1.5	99.0	0	++	0	0	0, 16 dys.	S,	S.	S.	0	0	+

## FOURFUL CASES—(Continued)

2354 F.	17	Good...	F. h. neg.; no expo.; bronchitis for 15 years; slight dulness and suppression of b. s. at r. apex.	1 exam. 0	1.5-1.2	101.4	+	+	+	0	0, 22 dys.	0	+	++	0	...	+
2343 F.	23	Good...	F. h. neg.; no exposure; pain in chest and some cough; indefinite physical signs at l. apex.	1 exam. 0	1.5-1.5	100.4	+	++	+	0	0, 23 dys.	0	S.	S.	0	....	0
2369 M.	29	Good...	F. h. neg.; no exposure; cough for 7 years, but worse recently; slight dulness and diminished b. s. at r. apex.	1 exam. 0	1.5-1.5	101.2	+	++	+	0	? Eyes +; skin +; 5 mos.	0	+	++	0	....	0
2332 M.	21	Good...	F. h. neg.; no exposure; cough for 3 mos.; secondary syphilitic eruption appeared after resection; neg. physical exam.	1 exam. 0	1.5	101.0	++	++	+	+	0, 44 dys.	S.	S.	+	0	....	0
2252 M.	23	Good...	F. h. neg.; no exposure; grip 12 days before and cough since; slight dulness r. apex and prolonged expiration.	None ..	1.5-1.5	102.4	++	+	+	0	0, 14 dys.	S.	+	+	0	....	0
1732 F.	16	Good...	F. h. neg.; no exposure; cough and expect. for 3 weeks; slight dulness and interrupted b. s. at r. apex.	1 exam. 0	1.5-1	99.6	+	+	+	0	0, 35 dys.	0	+	+	0	....	+
3040 F.	36	Good...	H. has pulmonary tb.; cough and sputum for 1 mon.; no definite physical signs.	1 exam. 0	1.5-1.5	100.6	+	+	+	0	0, 50 dys.	0	0	+	+		
2307 M.	14	Good...	F. h. neg.; no exposure; cough and sputum for 2 mos.; no definite physical signs.	4 exam. 0	1.5-2.5-10	99.4	0	?	+	0	0, 22 dys.	0	0	+	0	....	0
2343 F.	42	Fair...	M. died of pulm. tb.; cough for 2 mos.; no definite physical signs.	1 exam. 0	1.5-1.5-10	99.0	0	+	+	0	0, 6 mos.	+	+	+	0	+	
3245 M.	41	Good...	F. h. neg.; men in same shop have died of tb.; cough for 9 mos. with streaks of blood in sputum; slight dulness and few crackling rales at both apices.	1 exam. 0	1.5-1.5-10-10	98.6	0	+	+	0	0, 19 dys.	0	+	++	++		
2975 M.	16	Good...	F. has tuberculosis; cough for 4 years, worse recently; slight dulness and wavy inspiration at both apices.	0	1.5-1.5-10	99.0	0	+	+	0	0, 41 dys.	0	S.	+	0	....	0



Disp. No.	Sex.	Age.	General Condition.	History and Examination.	Sputum.	Subcutaneous Injections.							Skin Reaction.		Conjunctival Reaction.				
						Doses of Tuberculin.	Highest Temp.	Constitutional Reaction.	Local Reaction.	Focal Reaction.		Flare-up of Skin or Eye.	1%	5%	20%	1st.	Instillation.		
										Symptoms.	Signs.						2%	5%	3d.
2297	F.	20	Good..	F. h. neg.; no exposure; slight cough and pain in chest for 11 mos.; slight dullness at r. apex and prolonged expiration.	None	1.5-1.2-1.3	101.0	++	+	0	0	0, 11 dys.	0	+	++	0	0	....	0
2440	F.	26	Good..	F. h. neg.; no exposure; some cough and sputum for 2 mos.; note imp. at r. apex; b. s. exaggerated; few fine râles.	2 exam. 0	1.5-1.2-2.5-10	99.0	Slight.	+	0	0	0, 35 dys.	++	++	++	0	0	....	0
2538	F.	15	Fair..	F. h. neg.; no exposure; nocturnal cough for 9 weeks; dullness at r. apex and l. base; b. s. diminished; few moist râles.	1 exam. 0	1.5-1.2-1.3	99.4	++	++	0	0	0, 20 dys.	0	S.	++	0	+		
2306	M.	36	Good..	F. died with cough; no other exposure; cough for 1 year and recently worse; streaks of blood in sputum; slight dullness and diminished b. s. and fine crackles at r. apex; emphysema.	4 exam. 0	1.5-1.2-3.5	99.2	+	+	0	0	Eye ++; skin ++; 40 dys.	+	++	+++	+	+		
2437	M.	21	Fair..	F. h. neg.; a friend has tb.; cough for 1½ yr.; worse recently; dullness, diminished b. s. and some fine râles over r. u. lobe.	2 exam. 0	1.5	100+	+	++	+	0	0, 11 dys.	0	0	++	0	0	....	+
2396	M.	11	Fair..	F. h. neg.; no exposure; headache, fever and general constitutional symptoms for 3 wks.; no definite physical signs.	None	1.10-1.5-1.2-2	103.0	+++	+	0	?	0, 24 dys.	+	++	+++	+			
2642	F.	16	Good...	F. h. neg.; no exposure; cough and sputum for several mos.; no definite physical signs.	1 exam. 0	1.5	100.0	++	+	0	?	0, 37 dys.	0	++	+++	0	....	0	++

## PROBABLE CASES--(Continued)

PROBABLE CASES

Disp. No.	Sex.	Age.	General Condition.	History and Examination.	Sputum.	Subcutaneous Injections.						Skin Reaction.			Conjunctival Reaction.								
						Doses of Tuberculin.	Highest Temp.	Constitutional Reaction.	Local Reaction.	Focal Reaction.		Flare-up of Skin or Eye.	1%	5%	20%	1st.	2d.		3d.				
										Symptoms.	Signs.						2%	5%		1%			
2227	F.	20	Good...	F. h. neg.; no exposure; slight cough and pain in chest for 11 mos.; slight dullness at r. apex and prolonged expiration.	None ..	1.5-1.2-1.3	101.0	++	+		0	0	0, 11 dys.	0	+	++	0	....	0	0	2%	5%	1%
2440	F.	26	Good..	F. h. neg.; no exposure; some cough and sputum for 2 mos.; note imp. at r. apex; b. s. exaggerated; few fine râles.	2 exam. 0	1.5-1.2-2.5-10	99.0	Slight.	+		0	0	0, 35 dys.	++	++	++	0	0	....	0	....	0	....
2538	F.	15	Fair...	F. h. neg.; no exposure; nocturnal cough for 9 weeks; dullness at r. apex and l. base; b. s. diminished; few moist râles.	1 exam. 0	1.5-1.2-1.3	99.1	++	++		0	0	0, 20 dys.	0	S.	++	++	0	+		0	+	
2505	M.	36	Good.	F. died with cough; no other exposure; cough for 1 year and recently worse; streaks of blood in sputum; slight dullness and diminished b. s. and fine crackles at r. apex; emphysema.	1 exam. 0	1.5-1.2-3.5	99.2	+	+		0	0	Eye ++; skin ++; 10 dys.	+	++	++	+	+		+	+		
2437	M.	21	Fair.	F. h. neg.; a friend has tb.; cough for 1½ yr.; worse recently; dullness, diminished b. s. and some fine râles over r. u. lobe.	2 exam. 0	1.5	100.1	+	++		+	0	0, 11 dys.	0	0	++	++	0	0	....	0	....	+
2306	M.	11	Fair...	F. h. neg.; no exposure; headache, fever and general constitutional symptoms for 3 wks.; no definite physical signs.	None ..	1.10-1.5-1.2-2	103.0	+++	+		0	?	0, 24 dys.	+	++	++	+	+		+	+		
2612	F.	16	Good...	F. h. neg.; no exposure; cough and sputum for several mos.; no definite physical signs.	1 exam. 0	1.5	100.0	++	+		0	?	0, 37 dys.	0	++	++	++	0	....	0	....	0	++

## PROBABLE CASES—(Continued)

2286	F. 40	Good...	M. died of pulm. tb.; some cough off and on for a year; dullness, harsh b. s. and definite moist râles at r. apex.	1 exam. 0	1-5-1-3-5	99.0	Slight.	+	+	0	0, 50 dys.	S.	S.	0	0	....	0
2694	F. 23	Good...	M. died of pulm. tb.; no definite symptoms; note little imp. at both apices and b. s. harsh; few fine râles.	None	1-5-1-3-5	?	+	+	0	0	0, 26 dys.	++	++	0	+		
2689	F. 29	Good...	M. died of tb.; h. has tb.; general ill health for a year; no definite physical signs.	1 exam. 0	1-5-1	101.0	++	+	0	0	Eye ++; skin 0; 11 dys.	++	++	0	....	++	
3055	M. 13	Good...	F. h. neg.; no exposure; cough and expect. for 1 mo.; no definite physical signs.	1 exam. 0	1-5-1	100.0	Slight.	+	0	0	0, 55 dys.	+	+	0	....	+	
3071	F. 43	Fair...	F. h. neg.; no exposure; spat up a little blood 2 weeks before; slight dullness and diminished b. s.; fine râles at r. apex.	2 exam. 0	1-5-1	100.6	+	+	0	0	Eye ++; skin ++; 27 dys.	+	++	++			
3041	M. 21	Good...	F. h. neg.; no exposure; cough and hemoptysis; dullness, prolonged exp. and moist râles at r. apex.	1 exam. 0	1-5	99.8	+	+	0	0	0, 13 dys.	++	++	++			
1483	M. 41	Fair...	F. h. neg.; no exposure; grip 3 wks. before, followed by languor, night sweats, fever and cough; exp. prolonged at apex and few fine râles.	1 exam. 0	1-5-1-5	100.4	+	++	0	0	0, 16 dys.	0	+	0	....	0	
3345	F. 22	Fair...	F. h. neg.; no intimate exposure; cough and heaviness in chest for 6 mos.; no definite physical signs.	1 exam. 0	1-5-1	100.2	+	+	0	0	Eye ++; skin ++; 23 dys.	+	++	0	....	+	
3379	F. 15	Good...	F. h. neg.; no exposure; cough and a little sputum for 3 mos.; dullness and harsh b. s. and a few moist râles at r. apex.	2 exam. 0	1-5-1-5-10	100.0	+	+	0	0	0, 29 dys.	+	++	++			

PROBABLE CASES—(Continued)

Disp. No.	Sex.	Age.	General Condition.	History and Examination.	Sputum.	Subcutaneous Injections.							Skin Reaction.			Conjunctival Reaction.					
						Doses of Tuberculin.	Highest Temp.	Constitutional Reaction.	Local Reaction.	Focal Reaction.		Flare-up of Skin or Eye.	1%	5%	20%	1st.	Instillation.				
										Symp. toms.	Signs.						1%	2%	5%	3d.	
3392	M.	20	Good ..	F. h. neg.; no exposure; fever, cough and pain in chest 5 wks.; note dull and b. s. harsh with prolonged exp. at r. apex.	1 exam. 0	1.5-1.5	99.0	+	+	0	0	Eyes+++; skin +; 27 dys.	0	0	+	0	....	+	0	....	1%
3154	M.	24	Fair...	One S. died of tb.; 1 b. has had tb.; cough and expector. following a cold 1½ yr. back; dullness and suppressed b. s. at both apices and blowing exp. at r.	3 exam. 0	1.5-1.5	99.4	+	++	0	+	Eyes+++; Skin 0; 25 dys.	0	+	+	+	0	....	0	....	0
3228	F.	26	Good...	One B. has tb. and 1 s. coughs; cough for 2 mos. and indigestion; slight dullness at both apices with suppressed b. s. and crackles after cough.	None ..	1.5-1	100.0	+	++	0	0	Eyes +; skin 0; 13 dys.	+	++	++	+	0	....	++	....	++
3231	F.	19	Good...	One B. has tb.; visits him frequently; cough for 1 mo. and pain in the side; no definite physical signs.	1 exam. 0	1.5-1.5-10	99.8	+	+	0	0	Eyes +; skin +; 23 dys.	0	+	+	+	0	....	0	....	0
2763	F.	29	Good...	F. h. neg.; no exposure; cough and hemoptysis for 1 year; dullness, diminished b. s. and numerous moist râles over r. lower lobe.	4 exam. 0	1.5-1.5-10	99.0	0	0	0	0	0. 27 dys.	0	0	S.	0	....	0	....	0	....

INCIPIENT CASES

2413	M.	18	Good...	F. h. neg.; no exposure; cough and sputum for 6 mos.; streaks of blood in sputum; dullness and rough b. s. and a few moist and sonorous râles at r. apex.	3 exam. 0	1.5-1.2-1 -2	104.0	+	+	0	+	Eyes +; skin +; 17 dys.	0	0	++	0	0	....	0
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# INCIPIENT CASES—(Continued).

INCIPIENT CASES—(Continued).																
2512 F. 16	Good...	F. h. neg.; no exposure; cough and sputum for 2 mos.; dulness and blowing exp. at r. apex.	+ ?	1.5-1.2-2.5 -10	99.0	0	+	0	0	0, 5 mos.	++	++	++	++	++	0
2939 M. 27	Good...	F. h. neg.; no exposure; cough and exp. for 1 yr. and loss of weight; dulness, coarse b. s. and fine râles at r. apex.	3 exam. all +	1.5-1.5-10	99.6	Slight.	+	0	+	0, 27 dys.	+	+	++	+	+	0
2996 M. 23	Good...	Tb. in f.'s family; no exposure; cough and blood in sputum for 2 yrs.; sl. dulness and rough b. s. at r. apex and moist râles above and below clav.	1 exam. 0	1.5-1.5	101.2	++	+	+	+	Eye ++; skin ++; 20 dys.	+	++	++	+	+	0
2777 F. 27	Fair...	One S. died of tb.; some exposure; for 1 yr.; cough and sputum and a few moist râles at r. apex.	+	1.5-1	100.8	+	+	0	+	0, 36 dys.	+	+	++	+	+	0
2808 F. 39	Fair...	H. died of tb. and patient nursed him; fever and some cough off and on for 4 yrs.; slight dulness and suppr. b. s. at r. apex; fine râles at both apices.	1 exam. 0	1.5-1.5	101.2	++	++	0	+	0, 7 dys.	0	S.	S.	+	0	0
2838 F. 20	Fair...	F. h. neg.; intimate with a friend who had tb.; cough and sputum for 1 yr., and hemoptysis; sl. dulness; diminished b. s., with prolonged exp. and a few râles at r. apex.	1 exam. 0	1.5-1.2	99.8	+	++	+	+	0, 7 dys.	0	S.	+	+	0	0
3216 M. 21	Good...	F. h. neg.; intimate exposure; hemoptysis while in perfect health; dulness, diminished b. s. and numerous moist râles over l. lower lobe.	2 exam. 0	1.5-1.5	100.0	+	+	0	+	Eye 0; skin ++; 14 dys.	0	+	+	+	0	0
3215 F. 20	Fair...	F. h. neg.; no exposure; cough, sputum and hemoptysis; dulness at r. apex and a few râles.	None	1.5-1.5	100.0	+	+	?	+	0, 28 dys.	0	0	0	0	0	0

\*In this column M. means mother; F., father; F. h., family history; B., brother; S., sister; H., sounds; imp., impaired; exp., expiration.  
†The number of days or months in this column indicates the last subacute instillation and the day of giving the last subacute.  
‡S. in this column means sick.

\*In this column M. means mother; F., father; F. h., family history; B., brother; S., sister; H., husband; b. s., breath sounds; imp., impaired; exp., expiration.  
 †The number of days or months in this column indicates the length of time between the giving of the last conjunctival instillation and the day of giving the last subcutaneous injection.  
 ‡S. in this column means slight.

other two examinations were negative. The history and physical signs certainly suggest very strongly an early pulmonary tuberculous lesion.

In the 8 cases with definite focal reaction, 2 patients reacted and 6 were negative to the 1 per cent. conjunctival instillation. Of the 6 negative cases, 5 remained negative to a second instillation of 5 per cent. and 1 to a second instillation of 2 per cent. and a third instillation of 1 per cent. Seven patients gave definite skin reactions and one a slight skin reaction. In the incipient case negative to tuberculin subcutaneously, the patient gave a marked cutaneous reaction, but was negative to 1 per cent. and 2 per cent. in the conjunctiva.

In the 11 cases negative to tuberculin subcutaneously, 1 patient gave a conjunctival reaction to 1 per cent., 1 more to 2 per cent., and a third to 5 per cent. One gave no skin reaction and 2 only slight skin reactions.

Of the 2 patients giving doubtful reactions, both were negative to 1 per cent. and 2 per cent. conjunctival instillations and to a third instillation of 1 per cent. One gave a marked skin reaction, the other a slight reaction.

Of the 26 with a positive febrile and constitutional reaction, but without signs of a focal reaction, 6 were positive and 20 negative to the 1 per cent. conjunctival instillation. Of the 20 negative, 4 received a second instillation of 2 per cent. and 2 reacted, and 16 a second instillation of 5 per cent. and 7 reacted. Two of the patients negative to 2 per cent. received a third instillation and 1 reacted, and 1 patient negative to 5 per cent. reacted to the third instillation. All the 26 patients but one gave a definite skin reaction.

Table 11 shows, then, that there is no absolute agreement between these three methods of administering tuberculin. A patient may react to tuberculin subcutaneously and give no skin or conjunctival reaction and may give even a marked conjunctival reaction and fail to show any response to 10 mg. subcutaneously. On the whole, however, there is a much more constant agreement between the subcutaneous and the cutaneous reaction than between the subcutaneous and the conjunctival.

#### REPEATED INSTILLATIONS IN THE SAME CONJUNCTIVA

It has become a matter of common observation how frequently a conjunctiva which shows no reaction to an instillation of 1 per cent. will react when a second application of the same strength or even of a much weaker solution is made. Rosenau<sup>7</sup> instilled a drop of 1 per cent.

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7. Rosenau (M. J.) and Anderson (J. F.): Ocular reaction to tuberculin; a warning. *Jour. Am. Med. Assn.*, 1908, L, 961.

solution of tuberculin in the conjunctiva of 12 healthy men and none reacted. After fifty-one days a second instillation of the same strength or in a few cases of a weaker solution was made and 10 reacted definitely. Vaughan<sup>8</sup> instilled tuberculin into the conjunctivæ of 110 healthy students. Six reacted. Twenty-one days later a second instillation was made into the same conjunctiva and 59 per cent. reacted, some violently. Evidently one application of tuberculin highly sensitizes the local cells to subsequent contact. The reaction is probably analogous to the general tuberculin reaction and is at present best explained by the hypotheses of Wolff-Eisner<sup>4</sup> and Vaughan.<sup>9</sup> Vaughan has been able to split proteids into two substances, one toxic and the other inert. The toxic substance produces symptoms very similar to those of a tuberculin reaction. The inert substance, while itself devoid of poisonous properties, sensitizes an animal to subsequent injections of the proteid from which it is derived. This hypersensitiveness is highly specific, so that an animal sensitized to egg albumin will react to this proteid alone and to no other. When tuberculin is first brought in contact with the body cells there are so few receptors present to unite with the sensitizing moiety that the proteid is broken up too slowly for the poisonous substance to produce either local or general symptoms. Following this primary stimulation, however, the cells give off antagonistic bodies in such abundance that when tuberculin again comes in contact with them they seize on it with great avidity and the toxic portion is liberated so rapidly that its full poisonous properties come at once into evidence. It requires from seven to twelve days for the sensitiveness to become established and it may persist for many months. In our series, 33 patients negative to 1 per cent. and to either 2 per cent. or 5 per cent. received a second instillation of 1 per cent. in the eye previously negative to a drop of the same solution. Thirteen reacted and 20 remained negative. In 19 negative cases the time interval between the first and second instillation was two days in 5 cases, four days in 2 cases, five days in 2 cases, six days in 2 cases, seven days in 4 cases, eight days in 1 case, thirteen days in 1 case, twenty days in 1 case and ninety-five days in 1 case. In 11 positive cases the time interval was two days in 3 cases, four days in 1 case, five days in 1 case, six days in 2 cases, seven days in 1 case, nine days in 1 case, thirteen days in 1 case, and seventeen days in 1 case.

Although it may truthfully be said that we would have obtained a higher percentage of reactions had the interval between the two instilla-

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8. Vaughan (Victor C.): Discussion on papers of Drs. Evans, Wheaton and Smithers and Walker. *Jour. Am. Med. Assn.*, 1909, *lii*, 34.

9. Statement made at International Tuberculosis Congress, Washington, 1908.



tions been longer, still this is not the sole explanation of all of the negative cases. In 8 cases in which the patients did not react, the interval was at least a week. It has been definitely shown, notably by Roepke,<sup>10</sup> that, no matter how many successive instillations we may make, a certain number of cases will remain negative. The important clinical question arises whether we can ever sensitize the conjunctiva of a non-tuberculous individual. A large proportion of healthy people will react to repeated conjunctival inoculations, but so will they to subcutaneous injections, and we look on these individuals, not as sensitized by the repeated injections, but as possessing somewhere in the body a hidden tuberculous focus. Without such an assumption, we can find no satisfactory explanation for the persistently negative cases. We have ourselves never been able to sensitize the conjunctivæ of healthy rabbits to tuberculin by repeated instillations of varying strengths of and even of pure tuberculin. Such results in rabbits, however, can not be accepted as conclusive. For some reasons their conjunctivæ seem insensitive to tuberculin under all conditions, as the experiments of Hamill, Carpenter and Cope,<sup>11</sup> and of Nobécourt and Mantaux<sup>12</sup> show. We ourselves believe that any reaction to tuberculin, even after repeated instillation, indicates the presence of a tuberculous lesion. The advisability of using such repeated instillations clinically is another question. Practically all investigators are against such use. But Roepke, who cites Bandelier as agreeing with him, holds out strongly not only for the importance, but for the necessity of making repeated instillations, if we are to obtain satisfactory results. It is unnecessary to reproduce Roepke's well-arranged and full tables. Briefly he finds that to a single instillation of from 0.5 per cent. to 2 per cent. old tuberculin 17.4 per cent. of patients in the incipient stage react, 42.7 per cent. of second-stage cases and 55.7 per cent. of the third-stage cases. With each subsequent instillation these percentages rise until to four instillations, beginning with 0.5 per cent. and ending with 4 per cent., 100 per cent. of the patients in the second and third stages react and 92.2 per cent. of the incipient. If these four instillations are all made in the same eye, 100 per cent. of the patients in the early stage react; if two are made in each eye, only 63 per cent. react. Roepke then concludes that, in order to obtain

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10. Roepke: *Beitr. z. klin. d. Tuberk.*, 1908, ix, 353.

11. Hamill (S. McC.), Carpenter (H. C.) and Cope (T. A.): A comparison of the von Pirquet, Calmette and Moro tuberculin tests and their diagnostic value. *THE ARCHIVES INT. MED.*, 1908, ii, 405.

12. Nobécourt and Mantaux: *Ophthalmo- et Cuti- réaction dans la tuberculose expérimentale du lapin*. Soc. de biol. de Paris, séance du 26 Octobre, 1907. Cited by Villaret and Fixier: *Rev. de la tuberc.*, 1908, series 2, v, 355.

definite and valuable results, at least four instillations should be made, and preferably all four in the same eye. Our results agree with those of Roepke, in that the smallest number of reactions occur in the incipient cases, and he is quite right to emphasize that it is the diagnosis of these cases that particularly concerns us. We seldom need tuberculin to make a diagnosis in moderately advanced cases and far advanced cases. His tables certainly make a strong plea for his contention. It needs to be emphasized, however, that the results we obtain with tuberculin are clinically only relative. Unfortunately, it always gives either too much or too little. If we use dilutions strong enough to make all tuberculous patients react, the number of reactions among healthy individuals rises so high that the method loses its value. If, on the other hand, we make the dilutions so weak that only a small proportion of healthy persons react, we find that the number of tuberculous patients reacting is so small that the method again loses its value. This is the weak point in Roepke's claim. He has tried the method on too few healthy individuals to have any control. Those who have made such comparisons find that repeated conjunctival instillations reduce the test to a proportion almost parallel with the cutaneous reaction. We must admit with Roepke that single conjunctival instillations give us too little, but it is true that his plan gives us far too much.<sup>13</sup>

#### THE PROGNOSTIC IMPORTANCE OF THE CONJUNCTIVAL AND CUTANEOUS REACTIONS

Wolff-Eisner<sup>14</sup> was the first to emphasize the value of the conjunctival and the cutaneous reactions in prognosis. He assumes from his results that the ability to react to the tests represents a high degree of resistance to tuberculous infection, and an inability to react, a want of such resistance. He asserts, indeed, that the most severe reactions occur in individuals without manifest tuberculous disease. In a person who is definitely tuberculous a severe reaction speaks for good resistance, a weak or no reaction for poor resistance, and, other things being equal, the one with good reacting power will make a better fight against the disease than the one with poor or no reacting power. In support of this view, he finds that patients in the early or I stage give a higher percentage of reactions than the II, and the II higher than the III.

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13. For an attack on Roepke's views see Wolff-Eisner: *Ueber meine Ergebnisse bei Kutan und Konjunktival Reaktion*. *Beitr. z. Klin. d. Tuberk.*, 1908, x, 161. And for Roepke's reply, *ibid*, 1908, vi, 245.

14. Wolff-Eisner: *Beitr. z. Klin. d. Tuberk.*, 1908, iv, 1. Stadelman and Wolff-Eisner: *Deutsch. med. Wchnschr.*, 1908, xxxiv, 180.

These differences are very marked, 80 per cent. of early cases reacting and only 20 per cent. of the far advanced. Without at present offering any explanation of the divergence, we may point to our figures as giving almost the reverse proportion. Considering only the 1 per cent. instillations, we see from Table 7 that only 48 per cent. of the incipient cases react conjunctivally, while 71 per cent. of the moderately advanced and 69 per cent. of the far advanced react. One can not help but conclude from our figures that the duration and extent of the disease has an important influence on the reacting capacity of the individual.

TABLE 12.—CUTANEOUS AND CONJUNCTIVAL TUBERCULIN REACTIONS IN 27 INCIPIENT CASES.

	Strength of Tuberculin.	No. of Skin Reactions.			No. of Conjunctival Reactions.		
		1%	5%	20%	1%	2%	5%
Good general condition, 18 cases.	Negative reaction.	8	5	2	9	4	4
	Slight.	1	0	0			
	+	6	4	3	5		
	++	3	5	5	0		
	+++	....	4	8	4		
Fair general condition, 8 cases.	0	3	1	1	4	....	3
	Slight.	1	2	1			
	+	3	2	1	1	....	1
	++	1	2	3	2		
	+++	....	1	2	1		
Bad general condition, 1 case	0	1	....	..	1	....	1
	Slight.	....	1				
	+	....	..	1			
	++						
	+++						

It is true that there are more +++ reactions among the incipient cases, but if we add the ++ and +++ together (for these are all severe reactions) there is again a far higher percentage of severe reactions among the moderately and far advanced cases. There is not so striking a difference in the cutaneous reaction, but what difference there is is not strongly in favor of the incipient cases. Roepke comes to the same conclusion that we do. Wolff-Eisner so strongly attacks the diagnosis and classification of Roepke's material that we feel called on to say another word about our own. We feel this need particularly, as we

must admit the justice of much of Wolff-Eisner's criticism. In the first place he insists that Roepke places too much dependence on the subcutaneous tuberculin test to verify his diagnosis. 'We have elsewhere<sup>2</sup> spoken rather at length on this point and have insisted on how little value in the diagnosis of clinical tuberculosis is a positive tuberculin reaction without the accompanying signs of a focal reaction. Table 11 shows that we have not fallen into this error. We do, however, feel that we, too, are open to Wolff-Eisner's second count, namely, the

TABLE 13.—CUTANEOUS AND CONJUNCTIVAL TUBERCULIN REACTIONS IN 89 MODERATELY ADVANCED CASES.

	Strength of Tuberculin.	No. of Skin Reactions.			No. of Conjunctival Reactions.		
		1%	5%	20%	1%	2%	5%
Good general condition, 29 cases.*	Negative reaction. Slight.	9	2	2	9	....	3
		3	2	2			
	+	14	11	3	9	....	3
	++	3	11	9	7	....	4
	+++		3	13	3		
Fair general condition, 27 cases.	0	18	2		12	1	2
	Slight.	5	4	3			
	+	13	20	11	13	....	2
	++	1	10	14	7	....	1
	+++	....	1	9	5		
Bad general condition, 23 cases.	0	8	2	1	4	....	2
	Slight.	....	1	1			
	+	13	10	4	5		
	++	2	8	12	6		
	+++	....	2	5	8		

\* In the group of good condition only 28 patients received the 1 per cent. conjunctival instillation.

small number of cases showing tubercle bacilli in the sputum. This we know is not the fault of our cases, but due to the difficulty of getting sputum from ambulant patients and of having it satisfactorily examined in a busy out-patient clinic. Out of the 91 moderately advanced cases, sputum examinations are recorded in 67, of which number 47 were positive and 20 negative. Of the 20 negative cases, only 4 had more than one examination. This, I think, is a fair average for this stage of the disease. I may emphasize again that clinically we are sure of

every patient in the moderately advanced and far advanced groups. It must be admitted that a large individual factor does come into play in the diagnosis of incipient pulmonary tuberculosis. As we have stated, we have tried to eliminate this as far as possible. Knowing what we do about pulmonary tuberculosis, I think it would give figures equally, if not more false, to insist, as Wolff-Eisner does, that we are to include only cases in which there are tubercle bacilli in the sputum. This would largely destroy what we now call incipient cases, and if Wolff-Eisner has adhered to this criterion one fears that he may have obtained such a high percentage of reactions in what he calls the I stage, because he was really dealing with what we should call moderately advanced cases, and that he has gone to the opposite extreme in avoiding the premature diagnoses of Roepke.

TABLE 14.—CUTANEOUS AND CONJUNCTIVAL TUBERCULIN REACTIONS IN 81 FAR ADVANCED CASES.

	Strength of Tuberculin.	No. of Skin Reactions.			No. of Conjunctival Reactions.		
		1%	5%	20%	1%	2%	5%
Good general condition, 5 cases.	0	2					
	Slight.	....	1				
	+	3		1	2		
	++	....	3	2	1		
	+++	....	1	2	2		
Fair general condition, 22 cases.	0	9	5	3	6		
	Slight.	2	1	1			
	+	9	8	6	6	....	1
	++	2	7	5	7		
	+++	....	1	7	3		
Bad general condition, 54 cases.*	0	32	15	4	19	3	5
	Slight.	4	4	7			
	+	15	17	14	13	....	5
	++	3	16	14	17	....	1
	+++	....	2	15	4		

\* In the group in bad condition only 53 patients received the 1% eye instillation.

The number of our patients with tubercle bacilli in their sputum is too small to allow us to draw any final conclusions, but such as they are (see Tables 8 and 9) they by no means sustain Wolff-Eisner's views. There is, however, another way of looking at the prognostic value of

these tuberculin reactions. The disease may be early but progressing, it may be advanced but stationary. This is how Wolff-Eisner explains the negative reactions in the incipient group and the positive reactions in the advanced group. It is evident that, after all, this is the just way of considering the matter, for we know clinically that many patients in the advanced group with arrested lesions have much better prospects of living indefinitely than patients in the early stage with actively progressing lesions. In other words, the conjunctival and cutaneous reactions are to give us information, not so much about the stage of the disease as about the status of the fight between the individual and the disease. Until our cases have been observed for a longer period this point can not be decided, but some of the most severe reactions that we have witnessed were in the advanced cases which have since then rapidly progressed. Of course, in an ambulant clinic we rarely come in contact with moribund patients, and if one occasionally does make a visit he is not in condition to return the following day to have his eyes and arms examined. Many of our patients, however, are quite ill and have fever and sweats and other symptoms of advancing disease. It is notorious that moribund patients seldom react to tuberculin given in any way, and had we included a large number of moribund patients in our far-advanced class perhaps our figures would have been somewhat lower. Our far-advanced class does not give quite as many reactions as the moderately advanced.

TABLE 15.—DATA OF TABLES 12, 13, AND 14 CONDENSED AND STATED IN FORM OF PERCENTAGES.

Strength of Tuberculin.	Per Cent. of Skin Reactions.												Per Cent. of Conjunctival Reactions.					
	1%				5%				20%				1%				5%	
Degree of Reaction.	Neg.	+	++	+++	Neg.	+	++	+++	Neg.	+	++	+++	Neg.	+	++	+++	Nega- tive.	Posi- tive.
Good general con- tion.....	36	52	11	0	13	35	36	15	8	17	32	44	35	31	16	18	15	85
Fair general con- dition...	45	49	6	0	12	55	28	5	6	34	33	27	33	30	24	13	9	91
Bad general con- dition.....	53	41	6	0	22	42	31	5	6	35	33	26	31	23	30	16	12	88

By grouping our patients according to their general appearance and the state of their nutrition we thought some evidence might be gained on this question. This gauge we know is a rough one. But as a general thing patients that are progressing satisfactorily show it in their appearance; just as in a general way there will be more favorable prognoses among early lesions than among advanced—and proportionately

more cases to improve—so we find most of the patients in the incipient class in good general condition and most of the advanced in bad condition. Tables 12, 13, 14 and 15 give these results. There is distinctly a larger proportion of reactions among the patients in fair and bad general condition to the 1 per cent. skin test than among those in good condition, and about an equal proportion of eye reactions. There is even a larger percentage of severe eye reactions in the groups in fair and bad condition, although the severe skin reactions are higher in the class in good condition. The differences, however, are not large. Among the moderately advanced cases the number of patients is about equally distributed in the three groups (Table 13). There are more negative skin reactions in the good and fair classes than in the bad, although there are more severe reactions in the good. There are, however, more conjunctival reactions and more severe conjunctival reactions in the group in bad condition than in the group in good condition.<sup>15</sup>

#### SECONDARY CONJUNCTIVAL AND CUTANEOUS REACTIONS

It is now well known that patients who have had a conjunctival or a skin tuberculin test exhibit a marked tendency for these areas to flare up on subsequent subcutaneous injection of tuberculin. Such flare-ups may occur even when the primary application caused no reaction. In Table 11 the frequency of this phenomenon is shown and the time that had elapsed between the conjunctival instillation and the administration of the last subcutaneous injection. Considering the doubtful reactions negative, we have in 48 cases 14 negative and 34 positive reactions. In the 14 negative cases no patient showed a flare-up of either conjunctiva or skin, although all received at least 5 mg. of tuberculin subcutaneously. Three of the patients gave positive eye reactions and all but one positive skin reactions.

In the 34 positive cases, 8 patients gave both conjunctival and skin flare-ups, 3 only conjunctival and 1 only skin. In the patients giving both, the conjunctival recurrence was nearly always more severe than the cutaneous. Of the 11 patients with conjunctival flare-up, 7 had previously given a conjunctival reaction and 4 had not. Of the 9 patients with cutaneous recurrence all had previously shown definite reactions, although in a few instances the recurring reaction was more

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15. It is to be emphasized that these results speak neither against nor for Wolff-Eisner's hypothesis that tuberculin hypersensitiveness is a measure of tuberculosis resistance. There are many facts that speak against so simple an interpretation, but granting that Wolff-Eisner is correct, then our results indicate simply that the conjunctiva is an unreliable index of general tuberculin hypersensitiveness.

severe than the original. It is a noteworthy feature in the recurring skin reactions that the area of injection tends to be much wider than in the original reaction, while the infiltration is, as a rule, less marked. In several instances the 1 per cent. which had failed to show a reaction on the original application flared up during the constitutional reaction. We have no way of explaining why these secondary reactions occur in one instance and remain absent in another. The general condition of the patient, the extent of the lesion, the intensity of the original conjunctival or cutaneous reaction or the severity of the constitutional reaction seem to have no relation with it. The recurrence comes always after the dose liberating a general reaction. Although this general reaction need not be severe, a question of great scientific interest is whether these flare-ups following subcutaneous injections when the original instillation had been negative can ever occur in non-tuberculous individuals. We have ourselves observed them only in patients reacting to subcutaneous injections and have been unable to cause their appearance in healthy rabbits by injecting either small or large doses of tuberculin subcutaneously, even after the undiluted tuberculin had been dropped into the conjunctival sac.

#### THE DIFFERENTIAL CUTANEOUS REACTION

Detre<sup>16</sup> has described a so-called differential cutaneous reaction. This, in brief, consists in performing von Pirquet's test by the simultaneous application, in series, of human old tuberculin and of human and bovine bouillon filtrates. Then measuring the resulting reactions in millimeters, he believes himself able to draw reliable conclusions as to whether the patient has been infected with the bacillus of the human or bovine type, and as to whether the disease at the time of the test is active or latent. His theoretical premises are that a person infected with the human type of organism will react more strongly to the human filtrate than to the bovine, and *vice versa*. He also supposes that a patient exhibiting active signs of disease will yield a papule to the filtrate larger than or as large as the papule produced by the old tuberculin, and that the inverse relation will be found in patients with a non-progressive lesion. He thus differentiates acute and chronic human and bovine types and mixed types. That the human type may give a predominant and not necessarily an exclusive human reaction he attributes to some common properties of the bovine and human organisms. The predominant reaction to the filtrate in active cases he explains by the presence

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16. Wien. klin. Wchnschr., 1908, xxi, 173.



in the filtrates of a thermolabile toxin which is destroyed in the process of concentrating by heat the old tuberculin. To this toxin the body, according to him, is quickly sensitized during the process of a lesion, and with its arrest "autoimmunization" to this toxin occurs. Autoimmunization to the protein bodies of the old tuberculin he considers a rarer and more difficult occurrence.

Whatever is to be said as to the theoretical basis of Detre's work, we can not agree to the results obtained by him. Not only does our work strongly contradict his results, but we find, both in the nature of the phenomena and in his technic, serious objections to his procedure, and still more serious objections to his drawing conclusions therefrom. The whole structure of Detre's data and conclusions rests on the measurement of the diameter of the cutaneous reaction consequent on an abrasion by the boring method of von Pirquet. In looking over his tables, it can be seen that some of his cases are assigned their respective positions in the classification on the basis of a difference of only one or several millimeters in the diameter of the papule. Our own experience with the skin test makes us feel skeptical as to conclusions built on such minute differences as these. And the work of Schütz and Videky<sup>17</sup> strongly confirms us in our attitude. These authors, by careful measurements, by the application in series of tuberculins of varying strengths, by the application of the same solution in various parts of the body, have shown that the greatest variation in the size of the papules may result from no determinate factor. Using the same solution for several abrasions, they find large variation in the diameter of the papule—fully as large as the differences on which Detre stakes so much. In studying dilutions of various strengths, they find the same disappointing irregularity. In brief, they conclude that the difficulties in technic combined with the varied reactive and absorptive power of the different areas of skin make it impossible to use the size of the papule as a basis of anything respectable in inference. Von Pirquet,<sup>18</sup> too, states that variations below 50 per cent. in the diameter of a papule may be due to unavoidable differences in technic. Moreover, Schütz and Videky point out the great importance of remembering the various periods at which papules (even when due to the same tuberculin) reach their maximum. Assuming even that Detre's technic is all that we can not expect it to be, he has entirely neglected the time relations in deciding which is the predominant papule. What is the predominant papule to-day may not preserve that distinction to-morrow.

17. Wien. klin. Wchnschr., 1908, xxi, 1285.

18. Wien. klin. Wchnschr., 1908, xxi, 861.

We report, however, 150 cases in which tests were given somewhat according to his procedure. On the forearm four solutions were used in the following order: human O.T., bovine O.T., human bouillon filtrate, bovine bouillon filtrate, all undiluted. Borrowing Detre's nomenclature, the following classification is convenient:

Group 1.—The H. O. T. papule positive, the others slight or negative (old human lesion).

Group 2.—The H.O.T. more marked than the H.B.F. (old human lesion).

Group 3.—The H.B.F. more marked than the H.O.T. (active human lesion).

TABLE 16.—RESULTS IN 150 CASES WITH DETRE'S DIFFERENTIAL CUTANEOUS TEST.

	Non-tuberculous Cases.	Doubtful Cases.	Probable Cases.	Incipient Cases.		Mod. Advanced Cases.		Far Advanced Cases.		Total.
				Active.	Quiescent.	Active.	Quiescent.	Active.	Quiescent.	
Group 1.....	....	34	6	3	1	10	3	5	..	62
Group 2.....	....	5	1	1	..	2	..	2	..	11
Group 3.....	....	4	....	..	..	..	..	5	..	9
Group 4.....	....	1	....	..	..	..	..	..	..	1
Group 5.....	....	....	....	..	..	..	..	..	..	0
Group 6.....	....	23	1	1	..	4	..	4	1	34
Group 7.....	....	3	....	..	..	1	..	1	..	5
Group 8.....	....	22	1	..	..	4	1	..	..	23
Total.....	....	92	9	5	1	21	4	17	1	150

Group 4.—The B.O.T. and the B.B.F. positive, but the B.O.T. the more so. The others slight or negative (old bovine lesion).

Group 5.—Same as 4, but the B.B.F. more marked than the B.O.T. (active bovine lesion).

Group 6.—The H.O.T. and the B.O.T. equal and more intense than the H.B.F. and the B.B.F. (old mixed lesion).

Group 7.—The H.B.F. and the B.B.F. equal, but more intense than the H.O.T. and the B.O.T. (active mixed lesion).

Group 8.—All the papules approximately alike.

Table 16 shows the distribution of 150 cases in these 8 groups.

Groups 1, 2 and 3 would comprise, according to Detre, the human infection, equaling 54 per cent. of our cases.

Groups 4 and 5, comprising the bovine infection, contain together only one case, that is, 0.6 per cent. of our cases.

Groups 6, 7 and 8 embrace the mixed infection, 46 per cent. of our cases.

Detre's figures for his pulmonary cases are:

72 per cent. as compared with our 54 per cent. human.

19 per cent. as compared with our 46 per cent. mixed.

9 per cent. as compared with our 0.6 per cent. bovine.

Our results, as contrasted with his, point to the rarity with which the bovine papule predominates and to the frequency with which the bovine and the human papules are approximately alike.

Groups 3, 5 and 7 comprise all the active cases, according to Detre's conception—active human, active bovine, and active mixed.

Together these groups hold 9 per cent. of our cases. Group 5, active bovine, has not a single case. The active human group has 9 cases; the active mixed groups, 5 cases. Detre, in 57 cases, has 45 per cent. in the active group. Analyzed further, of our 47 advanced cases, 16 per cent. (7) are in the active group. Of our 107 early cases (embracing doubtful, probable and incipient cases), 6.5 per cent. (7) are in the active group. That is the group of cases in which he would expect to find the largest number of active reactions yields a smaller number than the advanced cases. Detre finds that of his cases with a lesion more than two years old 23 per cent. are in the active group; of cases with lesions less than two years old 82 per cent. are in the active group. The number of his cases is scarcely one-third of those in the above table. It will be noted that the great bulk of our 150 cases, 124 in fact, fall into Groups 1, 6 and 8—groups in which the old tuberculin has produced a papule larger or as large as the filtrates. It is also seen that the human O.T. tends to produce the larger papule.

These findings are in harmony with the results obtained in 150 of our cases other than the above, in which the human and the bovine old tuberculin were alone compared. The observation of these 150 cases was made before Detre's investigation came under our notice. It was undertaken in the hope of eliciting some therapeutic hints as regards the treatment of our patients which were not doing well on subcutaneous injections of human O.T. In only one of these 150 cases was the bovine reaction stronger than the human. In only 23 cases was the bovine reaction materially less than the human; in other words, the human and bovine old tuberculin tend to produce about the same sized papule. In all our readings we attempted no unjustifiable finesse or even measurements by rule. We decided predominance of a papule by its manifest

superiority over the rest. Lesser differences in either direction were ignored, for reasons above stated.

Our results indicate that if Detre's method is reliable pure bovine infection is rare with us, while mixed infection is surprisingly frequent and pure human infection surprisingly low. As regards activity, our results would indicate that the activity fails to exist where it ought to be. But we have little confidence in the method. All that the work seems to show is that the filtrate produces weaker reactions than the O.T.—a result opposed to Detre's.

In order to have made our tables strictly comparable to Detre's in regard to the question of activity and chronicity we should have used 20 per cent. O.T. instead of undiluted O.T. We have previously found, however, that the 20 per cent. O.T. yields practically the same papule as concentrated O.T. We must bear in mind also the work of Schütz and Videky. But, even assuming that 20 per cent. solution gives only a proportionate papule, we should expect, if Detre's statement as to the frequent predominance of the filtrate papule is true, that more than 9 per cent. of our total cases should show an active reaction.

There are not enough data at the present time to permit an estimate of the general opinion of workers with the differential cutaneous reaction. Hamill, Carpenter and Cope<sup>11</sup> have published but 24 cases. The strongest support to Detre's results is from Heim and John.<sup>19</sup> Von Gebhardt<sup>20</sup> finds that he can not confirm Detre's observation of the tendency of the filtrate papule to be as distinct as and even more distinct than the old tuberculin papule. He finds the latter nearly always predominant; in fact, according to him, the remaining papules show little tendency to appear at all, unless the O.T. papule is quite strong. Kentzler<sup>21</sup> finds the H.O.T. papule by far the most marked. Schütz and Videky, as has been stated, think the whole scheme illusory.

#### CRITICAL REVIEW OF THE VALUE OF THE CUTANEOUS AND THE CONJUNCTIVAL TESTS

In a previous article<sup>2</sup> we have dwelt on the limitations of the subcutaneous tuberculin test as a means of diagnosing pulmonary tuberculosis. So many healthy people have slight tuberculous foci somewhere in their body, and so many healthy people react to tuberculin, that the method gives positive clinical results only when there are present definite signs of a focal reaction. It is, then, desirable that there should be

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19. Heim and John: *Wien. klin. Wchnschr.*, 1908, xxi, 253.

20. Von Gebhardt: *Ztschr. f. Tuberk.*, 1908, xii, 345.

21. Kentzler: *Wien. klin. Wchnschr.*, 1908, xxi, 14.

some method of applying tuberculin which will elicit a reaction only in individuals with active disease. Knowing what we do about the relation of tuberculous infection to tuberculin hypersensitiveness, we can not hope that such an ideal method will ever be developed. Tuberculous infection does not mean that an individual has tuberculous disease, in the ordinary acceptance of the term "disease," for the behavior of the invading organism and the reaction of the besieged individual are so varied and so uncertain. It would seem impossible that tuberculin can ever give us unequivocal clinical information, and we have no right to demand it. A reaction simply means that the organism has developed a responsive activity to tuberculous infection, and it remains for experience to teach what relation this response bears to the activity and extent of the lesion. All tuberculin tests must, then, necessarily give clinically but relative results, and we feel that this relativeness must be thoroughly emphasized before any reasonable discussion can be had on their value.

In adults the cutaneous reaction has all of the disadvantages of the subcutaneous method and none of its advantages. The number of reactions in healthy individuals is just as high, and it never gives us information about the seat and extent of the lesion as do the focal reactions which frequently follow the subcutaneous test. Although the two do not run absolutely parallel, they nearly approach such correspondence, and a failure to react to either is of about equal significance, with, however, something in favor of the subcutaneous test. This want of reacting power means with the highest degree of probability the absence of tuberculous infection, a healed focus, or an overwhelming of the body by the infection, breaking down all defensive response. This latter group is, as a rule, easily recognized clinically. With the doubtful exception to which we have referred, we have never observed a definitely tuberculous patient fail to react to subcutaneous injections. We have never given tuberculin subcutaneously for diagnosis to patients in far-advanced cases. It is, however, well known that some of these do not react. Rarely a patient with tubercle bacilli in the sputum will fail to react to the skin test. Certainly there must be a great variation in the reacting power of different skins, and our present rough methods do not give uniform results, as von Pirquet<sup>22</sup> and Schütz and Videky<sup>23</sup> have so very strikingly shown. This might account for such occasional discrepancies. Attempts to get more accurate results by varying the

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22. Von Pirquet: *Verlauf der Allergie bei einen Falle von Masern und Miliiar Tuberkulose*. *Wien. klin. Wehnschr.*, 1908, xxi, 861.

23. Schütz and Videky: *Wien. klin. Wehnschr.*, 1908, xxi, 1285.

strength of tuberculin applied to the skin have been futile. A dilution to 1 per cent. gives fewer reactions among the healthy and doubtful patients, but fails utterly in the definitely tuberculous. A dilution to 5 per cent. is almost as unsatisfactory (see Table 7).

Our figures refer almost entirely to adults. In infants the cutaneous reaction has a much greater diagnostic value, decreasing in direct proportion to the age of the child. Von Pirquet's<sup>24</sup> table shows that 36 per cent. of children clinically not tuberculous from 5 to 8 years of age react. Only 4 per cent. react in the second half of the first year.

In reviewing the results obtained with the conjunctival test, the striking feature is the more favorable numerical results among the healthy or clinically non-tuberculous individuals, only 6 per cent. of the non-tuberculous patients reacting and only 25 per cent. of the doubtful. But 70 per cent. of the tuberculous react, however. Here we have conditions just the reverse to those of the cutaneous test. Instead of doing too much and showing so large a number of reactions among the non-tuberculous, the conjunctival test does too little and fails to give a reaction in many tuberculous cases. Of great interest is the comparison of the results in the different classes. It is important to repeat that the figures of Wolff-Eisner do not agree with ours, nor do those of von Muller,<sup>25</sup> Verdes<sup>26</sup> and many others, but those of Roepke and of Baldwin<sup>27</sup> do. Accepting our own figures, it appears evident that up to a certain degree the extent and the duration of the disease have a marked influence on the occurrence and severity of the reaction, and this influence is even greater than that of the patient's resistance, judged by such a rough measure as his general physical condition.

We feel that it would serve no purpose to quote a large series of figures from a large number of observers and point out how they agree with or differ from ours. Such compilations have been made frequently enough<sup>28</sup> and, besides, we doubt the value of these figures because they have mostly been gathered in an altogether indiscriminate way. There is usually, in the first place, entirely too little said about the character

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24. Von Pirquet: *Wien. med. Wehnschr.*, 1907, No. 28.

25. *Ber. der Tuberk. Aerzte Versamml. München*, 1908. *Centralbl. f. Tuberk.*, 1908, ii, 444.

26. *Cit. Centralbl. f. Tuberk.*, 1908, ii, 397.

27. *Internat. Tuberc. Cong.*, Washington, D. C., 1908; uncorrected leaflet.

28. See for literature, Smithies (F.) and Walker (R. E.): *Conjunctival tuberculin reaction as a means of diagnosis and control. Jour. Am. Med. Assn.*, 1909, lii, 25; also Engelbach (W.) and Shankland (J. W.): *Diagnostic value of the cutaneous and conjunctival tuberculin reactions. Jour. Am. Med. Assn.*, 1909, lii, 37.

of the material used and on what data the diagnosis rests. Knowing how large individual differences in diagnosis may be, we believe that this is an important matter. Of much greater significance, however, is the absolute lack of uniformity in the method of performing the test. Some use old tuberculin, others purified tuberculin, and dilutions range from 10 per cent. to 0.01 per cent. Mitulescu has estimated that a 1 to 10,000 solution of Hoechst's purified tuberculin is equal to a 1 to 1,000 solution of the Pasteur tuberculin or to a 1 to 250 solution of Calmette's tuberculin, and it has been shown that old tuberculin is still less potent than Calmette's. Some observers make a single instillation, others make a second instillation in the opposite eye, still others repeated instillations in the same eye, and some fail to tell in just what way they did proceed, as though the strength of the solution were the only factor of importance.

From our experience we are fully convinced that both the conjunctival and the cutaneous tests have an important place in the diagnosis of pulmonary tuberculosis. This value is enhanced by using the two tests together. When a patient fails to react to either test and there are no striking symptoms or physical signs of pulmonary disease, we feel that our negative diagnosis has received a valuable confirmation. If the eye is positive we feel that this is a strong indication that the patient has some active tuberculous focus; if symptoms and signs are present it is an important aid in excluding other pulmonary conditions; if they are absent it marks the patient as a suspect, and we should exhaust every means of investigation before sending him off with a negative diagnosis. It is these patients that we make an effort to observe and re-examine at stated intervals so that any change in their condition may be early noted. Certainly many of them never become manifestly tuberculous and they may remain well indefinitely, but we feel that they are at the time of reacting, in danger. No doubt there are others in even greater danger who fail to react, but as yet we have no method of discovering these, and we need not be less eager to help those that do. We feel that such a reaction is an important indication for treatment in a doubtful case. It is something definite about which we may focus more persistently, and more positively than we would otherwise do, hygienic changes in a patient's life that we are sanguine enough to believe may, in at least some instances, prevent the outcome which we fear. If the skin reaction is positive and the conjunctival negative we are thrown back unaided on our other clinical resources.

It should be fully emphasized that none of these tests can replace in the slightest degree a carefully taken history and a well-made exam-

ination. They can never stand censor over these; rather their value must ultimately be judged by them. They are aids and nothing more. They have been particularly serviceable to us in a busy clinic where many men are working and the individual patient can not always receive the prolonged and careful study he deserves. The absence of either skin or conjunctival reaction has in some cases incited us to the more careful observation that has led to reversal of an opinion too hastily given, and an unexpected conjunctival reaction to reaching a correct and early diagnosis.

Granting that the conjunctival reaction has the value we ascribe to it, it is of great importance to decide if such value is sufficient to justify its use in the face of the objections that are raised against it. In at least 1,500 instillations we have had but one untoward result, the patient developing phlyctenular conjunctivitis which subsequently completely healed. It might be objected that after receiving the tests many of our patients never return and that there may have been some accidents of which we have no knowledge. While this possibility must be allowed, we consider it highly improbable. It seems reasonable to presume that had any severe eye symptoms later developed the patients would have returned for observation, and they could not have gone to the eye clinic without being transferred by us. One is, however, obliged to consider with respect the many reports of severe and recurring conjunctival inflammations, of phlyctenular conjunctivitis and of corneal ulcers with permanent opacities. Some observers have had such accidents frequently, while others, and notably those who have used the test most, say they have seen no ill effects. It is important that many ophthalmologists take a stand against the test. Why results should be so divergent it is difficult to explain. Most of the unfavorable results have followed instillations in already diseased eyes or of too strong solutions, but this is not true of all the cases. Two of Schrumppf's<sup>29</sup> patients developed corneal ulcers after an instillation of 1 per cent. old tuberculin. Both were over sixty years of age. There are certain precautions that must be followed in making the test, and when these are observed accidents will be fewer. For at least the first instillation only a weak solution should be used, not over 1 per cent. old tuberculin, and we should think less than 0.5 per cent. of the precipitated tuberculin, although we have had very limited experience with the latter. The eyes should always be carefully inspected before the instillation is made, and

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29. Schrumppf: Ueber gefährliche Folgen der Calmetteschen Ophthalmoreactionen, München. med. Wchnschr., 1908, 1x, 2225.



the least abnormality regarded as a contraindication. A second instillation should never be made in the same eye. Considering the tendency of old people to conjunctival inflammation, and particularly to corneal ulceration, it were probably better to exclude these from the test. We think that our experience justifies us in continuing to use the conjunctival test after the method we have outlined and with the precautions indicated. This we have done since these data were compiled and have never had another untoward result.

A second objection is that a conjunctival instillation, whether there be a reaction or not, often renders subsequent administration of tuberculin subcutaneously for diagnosis or treatment, if not dangerous, at least unpleasant. At times a recurring reaction comes on after the dose given is not large enough to liberate a general reaction. This secondary reaction not only may be more severe than the first, but may be severe even though absent after the instillation. It is said that under tuberculin treatment constant recurrences may make injections very discomforting. Such manifestations during treatment, however, must be very uncommon. In a large number of cases we have never observed them. It is the diagnostic injections that are particularly influenced, and our tables show to what extent these recurrences follow. In only two instances were the conjunctival inflammations at all severe. If we feel that it is advisable to give subcutaneous injections to obtain a focal reaction, we believe a previous conjunctival instillation need not deter us. In our cases all such recurring reactions have promptly and satisfactorily subsided. It would be better, of course, to omit the conjunctival test in cases of patients to whom we wish to give tuberculin subcutaneously.

A word in regard to the method: What we aim to have is a dilution that is safe to use and still strong enough to give results worth having. We should certainly hesitate to put a stronger solution than 1 per cent. old tuberculin in the conjunctiva at the first instillation. Perhaps it will prove to be better to begin with a still weaker solution, but in our hands the 1 per cent. has proved safe and satisfactory. If a patient fails to react to this instillation we have some clue as to his tolerance for tuberculin and can then proceed to use a stronger solution in the other eye. What strength second solution shall finally be used remains to be determined. We have taken the upper limit of what we consider safety so as to get the largest number of definite reactions. We shall not use stronger solutions than 5 per cent. and we may with more experience come to use weaker. It is, indeed, a question open to discussion if much is gained by giving the second instillation. We feel that it is important

and point to our tables for demonstration. We use the old tuberculin instead of the precipitated tuberculin because it is more convenient and just as satisfactory. It has been claimed, too, that it is much more uniform in strength than the precipitated tuberculin.<sup>30</sup> Apparently slight differences in the method of preparation—for instance, in the length of time the alcohol is allowed to act on the tuberculin—give widely different results.

#### CONCLUSIONS

1. In adults the cutaneous tuberculin test is of value in diagnosis only when it is negative.

2. The frequency of its occurrence runs roughly parallel with that of the subcutaneous test.

3. The conjunctival test is of value principally on the positive side, a definite reaction indicating the presence of an active tuberculous lesion.

4. The most satisfactory results are obtained by using the two tests simultaneously. Both being negative speaks for the absence of any active tuberculous focus; both being positive, for its presence; the conjunctival negative and the cutaneous positive is no information of value.

5. We can not admit that the conjunctival or cutaneous reactions have any prognostic value.

6. The same conjunctiva should never receive a second instillation. The reaction so obtained is valueless for diagnosis and the procedure not without danger.

7. We believe that with proper precaution the conjunctival test may be used without danger of permanent injury to the eye.

8. We have been unable to confirm in any particular the claims Detre makes for his differential cutaneous reaction.

21 West Franklin Street.

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30. Hamill (S. McC.), Carpenter (H. C.) and Cope (T. A.): A comparison of the Von Pirquet, Calmette and Moro tuberculin tests and their diagnostic value. *THE ARCHIVES INT. MED.*, 1908, ii, 405. Smithies (F.) and Walker (R. E.): Diagnostic value of the cutaneous and conjunctival tuberculin reactions. *Jour. Am. Med. Assn.*, 1900, lii, 37.

## BUCKWHEAT-POISONING

WITH REPORT OF A CASE IN MAN \*

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Buckwheat-poisoning, or "fagopyrismus,"<sup>1</sup> may be defined as a disease which occurs in certain white or white-spotted animals that have been fed on the common buckwheat, *Fagopyrum esculentum* (*Polygonum fagopyrum*) or on the other species less frequently cultivated, *Fagopyrum persicaria*. Clinically, the milder forms of the disorder are associated with an itching erythema, situated mainly on the head and face, constipation and digestive disturbance, the more serious cases being attended by cutaneous, respiratory, febrile or urinary phenomena. Pathologically, there may be a vesicular, pustular, phlegmonous, or even gangrenous dermatitis, and inflammatory changes in the mucous membranes, the brain, nerves and lungs.

### CAUSES

The etiology of fagopyrismus presents several features which deserve careful consideration. The disease is most common in swine and sheep, especially in pigs and lambs. It is occasionally seen in cattle and goats, and is rarest in the horse. White or spotted animals are said to be exclusively affected. Those that are black or artificially blackened escape the disease, and, curiously enough, the pigmented parts of the skin in diseased white-spotted animals remain normal.

The worst cases of buckwheat-poisoning are seen in animals that have been fed on the buckwheat plant while in bloom, but the malady may develop after the eating of the grains, bran, chaff, straw or stubble. In winter the disease manifests itself merely by burning and itching of

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\*Read before the Johns Hopkins Hospital Medical Society, February 1, 1909.

1. Fagopyrismus is derived from the Latin *fagus*, beech; the Greek *pyros*, wheat, and the Latin suffix, *ismus*, a condition. Buckwheat is so named because of the resemblance in shape of its seeds to the triangular beech-nuts; hence the common name buckwheat and the botanical name "fagopyrum," both of which signify etymologically "beech-wheat." *Beech* and *buck* have the same root (cf. Ger. *buche*, beech; *buch*, buck—*buchweizen*, buckwheat; Anglo-Saxon *bok*, beech, buck; *bokwæte*, beech-wheat, buckwheat). The buckwheat plant belongs to the order of *Polygonacea* (*polys*, many and *gony*, knee). *Fagopyrum esculentum* (edible buckwheat) is the species most widely cultivated.

the skin. Some years it is more prevalent and severe than others. Locality seems to bear a causal relation. Sunlight is an important contributing factor, it having been generally observed that animals fattened on buckwheat under shelter or cloudy skies acquire the malady very rarely, and then in the milder form.

The immediate cause is unknown. Dammann<sup>2</sup> asserts that fagopyrismus is primarily a local disorder of the unpigmented skin, due to the disturbing action of fungi that live on buckwheat, or that it is caused by the poisonous products of these parasites. In support of this theory, he points out the readiness with which the exposed parts of animals may become infected by actual contact with the food during the act of feeding. Schindelka<sup>2</sup> believes that the disease arises from the intestinal absorption of toxic substances which are generated in buckwheat either as a result of bacterial change, or because of peculiar teluric conditions. He argues that these bodies become active only under the chemical influence of the sun's rays, and provided there is no pigment lining to act as a barrier.

In view of the causative relation of sunlight to the development of buckwheat-poisoning, it is of importance to note the recent work of Hausmann,<sup>3</sup> who, in a preliminary report on the "Sensitizing Action of Animal Pigments and Its Physiologic Significance," announces that bile possesses marked photodynamic power. He had previously shown that, under the influence of light, rapid hemolysis occurs when the extracts of chlorophyl plants are added to red corpuscles and that, on the other hand, no hemolytic action takes place if a similar mixture is kept in the dark. Experimenting with animal substances, he has found that prompt hemolysis results when bile is allowed to act on red cells in the presence of light. Control tests, in the absence of light, proved negative. Hematoporphyrin, he tells us, has even greater sensitizing properties, when activated by light, than bile itself. Hausmann also calls attention to the great resemblance of this photodynamic power of the extracts of chlorophyl plants to the photosynthetic assimilation processes of green plants as they occur in Nature. He also refers to the genetic relationship between hematoporphyrin and chlorophyl. In comparing their similarity, I have been struck with the fact that phyloporphyrin, a derivative of chlorophyl, not only closely resembles in structure the hematin derivatives, hematoporphyrin and mesoporphyrin, but that it

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2. Hutyra and Marek: *Spezielle Pathologie und Therapie der Haustiere*, 1906, ii, 828.

3. Hausmann: *Die sensibilisierende Wirkung tierischer Farbstoffe und ihre physiologische Bedeutung*. *Wien. klin. Wchnschr.*, 1908, xxi, 1527.

shows almost the identical absorption spectrum which is characteristic of these two hematin derivatives. And, further, it is of great interest to note that when phyloporphyrin and hematin are submitted to reduction with concentrated hydriodic acid both yield hemopyrrol, and that hemopyrrol is converted into hydrobilirubin by the action of sunlight.

The accompanying diagram brings out more clearly these points of resemblance.<sup>4</sup>

Hausmann<sup>3</sup> is of the opinion that we have much to learn regarding the causative relation of the sensitizing coloring materials of our bodies to normal and abnormal processes. He suggests as not improbable the sensitizing action of bacterial products, and the possibility that certain skin diseases are caused either by an excess or insufficiency of the sensitizer. This theory gives the hint that fagopyrismus may be due to the photodynamic power of some substance which becomes a sensitizer by virtue of the specific action of the sun's rays, and that the transformation takes place while it is slowly passing through the peripheral blood streams of animals having little or no cutaneous pigment; and, further, it may be assumed that this substance remains inert and harmless in the bodies of the black animals, because of the failure of the sunlight to activate it through dense pigment.

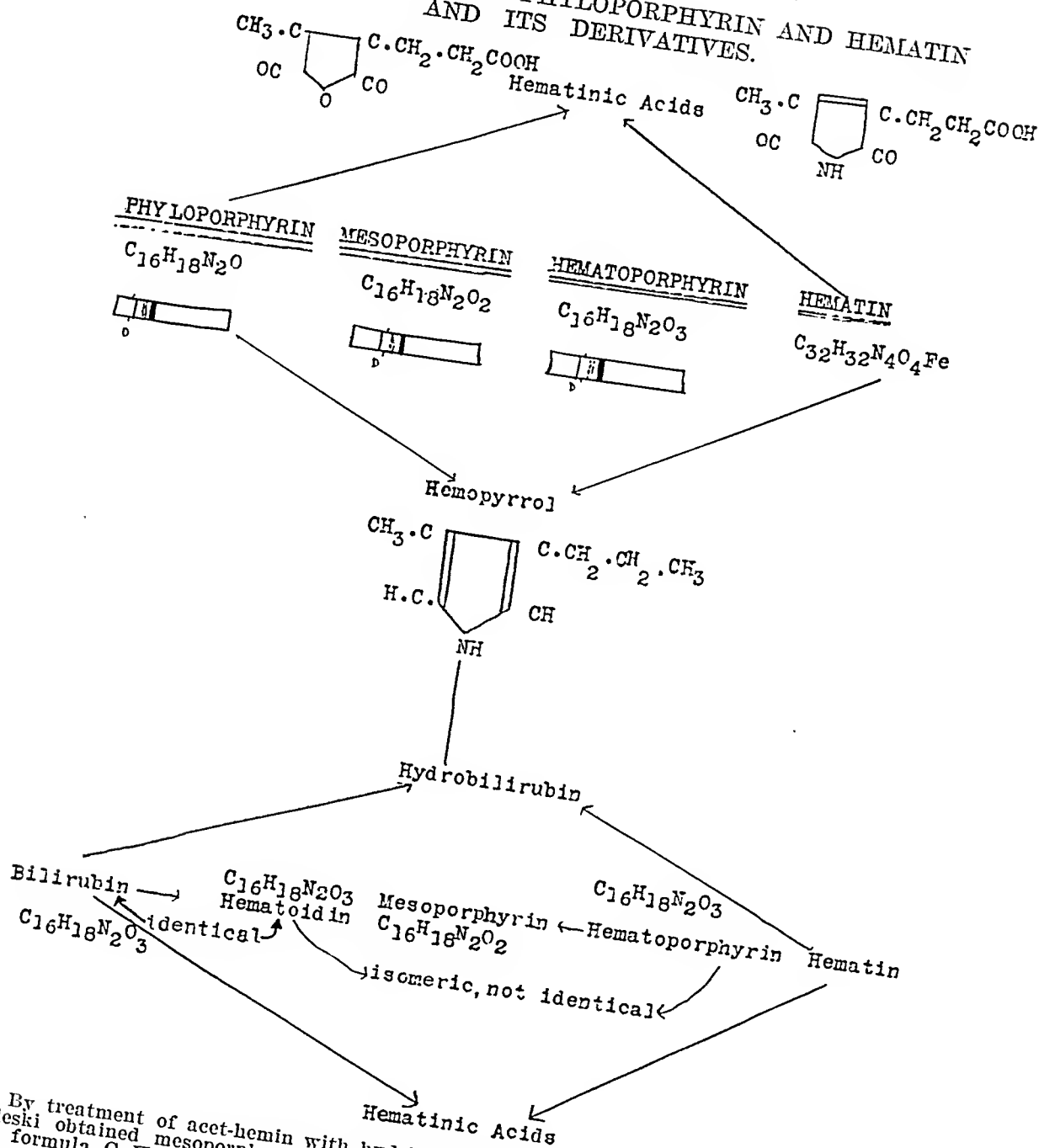
#### SYMPTOMS

In the milder form of buckwheat-poisoning in animals an erythematous rash occurs which is situated on the head and face, especially on the ears and eyelids. It may extend to the throat or manifest itself in any unpigmented part of the skin. There is more or less swelling and intense itching. The erythema is followed by a brownish desquamation and later by more or less pigmentation. The severer cases occur during spring and summer. The eruption may be vesicular in type—the so-called sheep-pock. The vesicles vary in size from a lentil to large blebs, which on rupture exude a clear straw-colored fluid. Crust formation follows, and there is finally slight pigmentation. The skin is hot and swollen. The itching is apparently intolerable. The swelling may be so marked as to cause the eyelids to close and the ears to hang down. There are other cases which are characterized by a pustular or a phlegmonous dermatitis (the head-erysipelas of sheep) or even a gangrenous

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4. Hematin, the prosthetic group of oxy-hemoglobin, is easily converted into hematoporphyrin, which latter shows a characteristic absorption spectrum. (The older and probably incorrect formulas are used, since they bring out the relations in a clearer manner.)

# RELATIONS BETWEEN PHYLOPORPHYRIN AND HEMATIN AND ITS DERIVATIVES.



By treatment of acet-hemin with hydriodic acid and phosphonium iodid, Nencki and Zaleski obtained mesoporphyrin, a substance having the composition represented by the formula  $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_2$  and giving an absorption spectrum closely resembling that of hematin but somewhat nearer the violet end.

By treatment of chlorophyll with alkalis phyloporphyrin is obtained, which has a chemical composition represented by the formula  $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}$  and which shows the same characteristic absorption spectrum as the two hematin derivatives but still nearer the violet end of the spectrum.

By oxidation of either phyloporphyrin or hematin Küster obtained two crystalline substances which he called hematinic acids and which were shown to be derivatives of pyrrol.

When submitted to reduction with concentrated hydriodic acid both phyloporphyrin and hematin yield hemopyrrol.

Hemopyrrol is converted into hydrobilirubin by the action of sunlight, and by suitable treatment both hematin and bilirubin can be made to yield the same substance.

The crystalline substance hematoidin, found in old blood clots, and surely derived from hematin, has been shown to be identical with bilirubin.

Like phyloporphyrin and hematin, bilirubin also yields the hematinic acids on oxidation.

form. Conjunctivitis, stomatitis, laryngitis and bronchitis more or less proportionate to the various skin lesions have been observed. The animals grow restless, wander aimlessly about and rub their bodies against hard objects. There are anorexia, retching, fever, dyspnea, cough, constipation, at times acute gastrointestinal disturbances and in some instances strangury. The group of cases showing marked disturbance of the nervous system may or may not be associated with skin lesions. Rabc<sup>5</sup> reports epileptiform seizures in swine and horses without any skin disorder. Some of the animals become maniacal, cry out and jump and run about in a wild, excited manner. Again, others show signs of disturbance of the central nervous system by one or more of the following phenomena: rotatory movements, vertigo, severe cramps of the voluntary muscles, tremor of the extremities or lips. There may be the opposite picture of depression, stupor, coma or paralysis of the spastic or peripheral type.

Richter<sup>6</sup> observed, in a number of swine that had been fattened on buckwheat, anorexia, dry stools, strangury, fever and dyspnea. In those that died there were found at autopsy inflammation of the mucous membrane of the stomach, inflammatory changes in the neck of the bladder (in one instance rupture of the viscus) and hyperemia of the lungs and brain.

Ergopyrismus may prove rapidly fatal in the cerebral form, or where there is urgent dyspnea due to the edematous narrowing of the air passages. Under proper management the symptoms usually subside promptly, but tend to recur after ten days or an even longer period if the animals are subjected to the blazing sunshine.

The treatment consists of immediate withdrawal of buckwheat as food, shelter from the sun, purgation, and locally the application of bandages saturated with cooling antipruritic lotions.

#### BUCKWHEAT-POISONING IN MAN

I have been unable to find any medical record of buckwheat-poisoning in man, except for the general statement in Gould's Medical Dictionary (see "buckwheat") that the free use of buckwheat tends to constipation, indigestion, headache and a peculiar roughness and itching of the skin. In 1897 von Jaksch<sup>7</sup> quoted Kobert as his authority for the

5. Friedeberger and Fröhner's *Veterinary Pathology*. Translation by Hayes, 1908, i, 458.

6. Fröhner: *Lehrbuch der Toxicologie für Thierärzte*, 1890, p. 213.

7. Von Jaksch: *Die Vergiftungen: Nothnagel's Spezielle Pathologie und Therapie*, 1897, 548. Also Kobert: *Lehrbuch der Intoxicationen*, Stuttgart, 1893, p. 443. For literature, *ibidem*, edition 2, 1906, ii, second half, p. 585.

statement that no case of buckwheat-poisoning had been reported in man. Poisoning has been observed in the human being from eating the common beechnut. The symptoms were vomiting, headache, dyspnea, spasms of the larynx, similar to those seen in hydrophobia, and unconsciousness.

Rakun<sup>s</sup> reported, in Petersburg, Russia, in 1899, two cases of poisoning, in a woman and her son, who developed restlessness, weakness, rapid pulse, dilated pupils, thirst, dryness of the throat and nausea, shortly after eating heartily of buckwheat gruel. The buckwheat in question had been bought at a neighboring grocery store—only just enough of it for the one meal. Rakun, however, went to the store, and, on examining that particular buckwheat there, found that it contained large quantities of henbane grains. He at once attributed the poisoning to the henbane and not to the buckwheat.

#### HISTORY OF AUTHOR'S CASE

The case of fagopyrismus which I have the privilege of reporting is that of a man who throughout his life has had a most remarkable hypersusceptibility to buckwheat. He has gray eyes and a fair skin. His history, which he has been good enough to give me in detail, is of sufficient importance, I think, to report in full, practically in his own words. He says:

My first acquaintance with buckwheat dates back to 1863, when, at the age of 9 years, I was taken by the district school teachers to participate in a spelling contest. About 10 o'clock in the evening I ate heartily of a supper which was prepared at a near-by farm house. Buckwheat cakes were served at the end of the meal. When I had eaten a small part of a cake I began to experience great discomfort in my throat, gullet and stomach—I felt as if I had swallowed hot lead. I at once attributed it to the piece of buckwheat cake because of its strong and strange taste to me, having never before eaten of the food. I could not swallow another mouthful of the cake, nor endure the retching caused by what I had already eaten. I was obliged to leave the table for the open air. One of the company followed me out and advised me to seek relief by running my finger down my throat. The effort it cost me to dislodge the offending morsel served further to distort my features, which had already become grotesque. My eyes were blood-shot, my face was red and swollen, and my lips were knotty with large hives.

Somewhat frightened by my condition and by the disquieting remarks my appearance called forth, I decided to go home. I lived on a frontier farm three miles distant. The night was very cold, but I found the zero temperature soothing to my hot and itching skin, and the long walk in the snow helped me to regain my composure.

On reaching home my mother questioned me closely. She attributed my condition to violent exercise rather than to something I had eaten, as there had been

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S. Rakun: Otravleni greehnevoi Krupoi. Feldscher. St. Petersburg, 1899, ix. 141. A translation of Rakun's report was kindly obtained for me by Major Walter D. McCaw, Librarian, Surgeon General's Office, Washington, D. C.



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an intermission of twenty minutes allowed the boys for exercise, and I had been particularly active, joining them in wrestling matches and in other strenuous games. I stoutly maintained that the piece of buckwheat cake had caused all of my suffering. The following morning I had fully recovered from all traces of my unpleasant experience.

For years afterward I occasionally had attacks similar in nature but milder in form. Each time my mother had made cakes, mush or hot bread from a particular grist of corn-meal. Inquiry at the mill developed the fact that the corn was ground on the same set of stones which had been used for grinding the grains of buckwheat.

When traveling I am always on my guard against being served buckwheat cakes, declining invariably cakes of any kind when buckwheat cakes are on the menu, for no matter how carefully the batter of wheaten or corn cakes is made, if the cakes are cooked on a griddle that has been previously used for cooking buckwheat cakes I can not eat them and retain them.

Twice I have been served with buckwheat cakes when other cakes were ordered, and each time I have suffered desperately, although but one mouthful was swallowed. On the last occasion I managed to reach a doctor, but, before starting for his office, I drank a bowlful of mustard water, and on my way stopped at a drug store where I was given two teaspoonfuls of the wine of ipecac. When I reached the doctor he was visibly startled by my appearance. He gave me two doses of hive sirup, but it was fully thirty minutes before the desired effect was obtained. This was the longest time I have suffered before vomiting occurred. The burning exceeded anything I had previously endured. My face, eyes, tongue, neck, shoulders and hands were hot, inflamed and swollen, and my lips were thick with hives. The itching about my neck, shoulders and chest was unbearable; my lungs felt as if they had so tightened up that I could hardly get my breath; I coughed incessantly; the saliva dripped from my mouth and I rolled about on the doctor's floor in agony. Almost immediately following the action of the emetic I began to shake like one in an ague fit—the reaction, I suppose. This attack happened on one New Year's morning, and to give you an idea of the rapidity of my recovery, I made several social calls in the afternoon. I may add that for several days following my worst attacks, the skin of my hands, scalp and face sheds in little pieces.

For a number of years I thought I had the same idiosyncrasy for black pepper and certain ground spices, having had the same distress after eating highly seasoned foods, as soups, turkey dressing and the like. To settle this point I bought pepper berries and had them ground at my home. No trouble followed their generous use. Suspecting some form of buckwheat to be the adulterant in the ground spices, I once asked an agent of a large spice mill if such was the case. After some hesitation he admitted that his firm bought buckwheat hulls by the carload and had them roasted, ground and mixed with spices, particularly with black pepper. I have met with this adulteration in pepper but rarely in recent years.

My salivary glands are so susceptible to the buckwheat poison that I can readily detect buckwheat adulteration in food by simply holding a portion of the suspected morsel under my tongue. If there is buckwheat adulteration my tongue swells and burns and there is prompt increase in the flow of saliva, and, it is needless to add, that since I have known the usefulness of this precaution no particle of food has been swallowed that showed the presence of buckwheat contamination.

Once I was made very sick by eating honey which I noticed was rather dark. On tracing up its source I learned that it was made by bees that were allowed to feed on the buckwheat blossoms, and that this particular kind of honey was known commercially as "buckwheat honey."

I am seized with long-continued sneezing attacks if exposed for a moment to buckwheat meal that has been scattered about in the dry state. I have frequently had such annoyance to follow brief visits to grocery stores where buckwheat meal had recently been handled. Just lately I had a severe attack of sneezing. It began as soon as I reached my office. I at once asked if any buckwheat was in the room. My clerk seemed surprised and said, "Yes, there is a bag of it over there in the corner." It had been sent to me, without my knowledge, by an acquaintance of mine who knew nothing of my unenviable idiosyncrasy.

All nuts, except almonds and Brazil-nuts, affect me in a manner somewhat similar to buckwheat, except that the salivary glands are not nearly so sensitive, nor is the effect on the lining of the stomach so immediate or severe. The tightening up of the lungs and bronchial tubes is, however, more marked than in the case of buckwheat poisoning, the symptoms being not unlike asthma in extreme cases.

#### EXPERIMENTS

At my request, the patient submitted to the three following experiments. I had thought of testing the sensibility of his conjunctiva by instilling into the eye a few drops of a weak infusion of buckwheat, but at the suggestion of Dr. William S. Thayer the skin test was substituted. The experiment was made by Dr. Rufus I. Cole in Dr. Thayer's office, about 10 o'clock on the morning of the 26th of last November.

The left arm was scarified in two places under strict antiseptic precautions. Without the patient's knowledge, an amount containing a grain of buckwheat was taken from a sterilized infusion of the cereal and rubbed into the upper scarification, while a mixture of sterile flour and water was applied to the lower one. The denuded areas were situated about three inches apart. As controls, Drs. Thayer, Cole and I underwent a like procedure with uniformly negative results.

Within fifteen minutes after the vaccination the patient remarked, "The buckwheat is beginning to work." He complained of a "tight feeling" in his chest, and of nausea in the "pit of the stomach." He began to cough at frequent intervals, and there was noted increase in the respiratory movements; asthmatic breath sounds; rapid pulse which soon became intermittent; suffusion of the conjunctivæ; an erythema, more pronounced on the face, neck, forearms, hands, chest and back than on the buttocks, abdomen and lower extremities; intense pruritus; slight swelling of the features, hands and fingers; giddiness, restlessness and unsteadiness in the gait. The pupils remained normal. There was no thirst. Because of the asthmatic symptoms, Dr. Thayer gave the patient 1/100 of a grain of nitroglycerin.

The dressings which had been applied to the arm were now removed, and it was found that only the upper scarification showed any local reaction. Here there was an urticarial wheal the size and shape of a half-dollar piece. About this time the heart's action became so irregular and labored that it was decided to prevent further absorption of the buckwheat by cleansing the vaccinated area. Notwithstanding the fact that 95 per cent. alcohol was used, the lower scarification became contaminated with the buckwheat washings from the upper one, resulting almost immediately in the formation of a round wheal about the size of a nickel. It was fully an hour and a half after the onset of symptoms before the patient was physically equal to leaving the office.

He was seen by me late in the afternoon. The wheals had subsided, but the skin surrounding the scarified points was distinctly blanched. An occasional drop in the pulse, slight itching and a faint erythema on the face and hands persisted. The conjunctivæ had cleared up; fever and urinary symptoms were absent. No scar followed the vaccination.

On the afternoon of December 30, Dr. Cole made a control experiment in his laboratory at the Johns Hopkins Hospital. The arm was again scarified in two places and applications were made. The patient submitted to this second test after being assured that he would be promptly relieved at the appearance of the first symptom by immediate washing of his arm. No local or general disturbance resulted. The pulse was taken by me at frequent intervals and was found to be rhythmic and normal throughout. As a matter of fact, unknown both to the patient and myself, sterile water only had been applied to the scarified areas. It was a little disappointing, however, that the patient failed to sneeze, though seated near a bench on which a small amount of buckwheat meal had been scattered.

The third experiment was performed by Dr. Cole in his laboratory on January 27, 1909. The object of this test was to determine the patient's sensitiveness to buckwheat by mouth. The buckwheat used was obtained by me at a grocery store where it was advertised as the "dark, old-fashioned kind." It was decided to give the patient in succession unknown powders, some of which contained buckwheat, and to observe whether or not any marked reaction followed the administration of the buckwheat-containing powders. For each test an amount of powder about equal to that which could be held on the end of a knife-blade was placed on the patient's tongue and allowed to remain there for from five to ten minutes when he was directed to spit it out and to rinse his mouth thoroughly before the next powder was given. A separate wooden spatula was used for each test, and care was taken to prevent any trace of buckwheat gaining admission to the powders not intended to contain it.

Mixtures of the following substances were made and sterilized in test-tubes, the ingredients of which were indicated by suitable letters on the labels as indicated in the following key:

C. = Cornmeal.  
F. = Flour.  
M. = Maltose.  
G. = Glucose.  
B. = Buckwheat.

*Test 1.*—The powder contained G., F., M. and B. The patient did not detect the buckwheat and said that he felt sure the powder contained none.

*Test 2.*—The powder contained G., M. and B. There was no marked reaction, but the patient had a sensation of warmth in his mouth. He suspected buckwheat, and said that he felt confident that vomiting would result if he swallowed the powder. There was beginning suffusions of the scleræ and slight redness and itching of the face and hands.

*Test 3.*—The powder contained C., M. and F. No increase in the symptoms was noted. The patient said that he thought the powder contained no buckwheat.

*Test 4.*—The powder contained F., M. and G. Patient coughed a little, and complained of a little burning in his mouth, but did not regard the test as positive. There was a little increased redness of the face. He complained of itching in his mouth.

*Test 5.*—Same as 2, which patient considered suggestive.

*Test 6.*—A very small amount of pure sterilized buckwheat was placed on the tongue. The patient considered this test free of buckwheat.

*Test 7.*—A larger amount of the same pure buckwheat was given. The patient complained of burning in his mouth, and said he felt as though he had had a very slight trace of buckwheat.

*Test 8.*—Same as 2. No increase in symptoms.

*Test 9.*—Same as 7. No definite reaction.

It was now thought that the buckwheat being used was not active. We decided, therefore, to substitute some of the sterilized buckwheat which had been used previously in the test by insertion into the scarified area on the patient's arm on November 26.

*Test 10.*—This buckwheat, equal in amount to that of any of the powders employed in the foregoing tests, was placed on the patient's tongue. No violent reaction followed. The patient was doubtful at first if this powder contained buckwheat, but later he expressed himself as confident of its positive nature. He felt like vomiting and said that he must sit down. There was increase in his cough and hoarseness developed. Suffusion of face and scleræ became more marked. He complained of itching and burning in his mouth, and there was some drooling; the buccal and pharyngeal membrane became intensely red. The erythema was particularly marked and persistent on the chin. There were also redness and intense itching of the hands and fingers. On the lower lip near the right angle of the mouth two typical wheals developed. The pulse, which had been regular, increased in rate of 100 and then became irregular, dropping a beat in every eight or ten beats. I accompanied the patient to his office. He complained of tightness in his throat and chest, also of heat and itching all over his body. The drooling and dysphonia became more marked, and by the time he reached his destination he could barely speak above a whisper. I saw him again in half an hour's time, and found him somewhat better, but it was several hours before the symptoms disappeared.

The subject of fagopyrismus opens up an inviting field for further investigation. I shall report later the result of a series of experiments I am about to begin on animals.

In conclusion, I desire to thank Drs. Thayer and Cole for the interest they have shown in the case and for their valuable and generous aid.

2537 St. Paul Street.

# STUDIES IN INACCESSIBLE INTERNAL HEMORRHAGES \*

CARL J. WIGGERS, M.D.

DETROIT

## II. THE INEFFECTIVENESS OF ADRENALIN IN PULMONARY HEMORRHAGE

### I. INTRODUCTION

The chief value of adrenalin in inaccessible hemorrhages consists in its ability to elevate the general pressure and direct a greater proportion of the blood still remaining within the body to the medulla, where its presence is needed to maintain the viability of the vital centers. To be practical in this capacity, it becomes imperative that it should not also increase the bleeding; in fact, it is desirable that hemorrhage should at the same time cease or diminish. In a recent research I showed that small doses of adrenalin (0.025 mg.), which I designated as "therapeutic doses," raised the pressure and diminished the bleeding from the intestinal vessels. In the present research the effect of adrenalin on pulmonary hemorrhages was investigated.

### II. PREVIOUS WORK

Cybulsky and Syzmonowicz<sup>1</sup> were probably the first to demonstrate experimentally that adrenalin slightly raised the pulmonary arterial pressure. Velich<sup>2</sup> later found that this slight rise of pressure also occurred in the left auricle, and drew the conclusion that it was due to the inability of the left heart to work effectively against so high an arterial pressure as adrenalin created. The facts thus brought out have served to condemn the use of adrenalin in pulmonary hemorrhages. The most complete study of this question was made by Plumier<sup>3</sup> in 1904. He also found a rise of pulmonary arterial and left auricular pressures, evidently due to a "back effect," as the damming back of blood into the pulmonary circuit has been styled. He showed further, however, that this "back effect" occurred only when adrenalin slowed the heart. When a slowing of the heart was prevented by vagus section, the pressure

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\*From the Research Laboratory of Parke, Davis & Co.

1. Cybulsky and Syzmonowicz, quoted by Plumier: *Jour. de physiol. et de path. gén.*, 1904, vi, 655.

2. Velich: *Wien. med. Wchnschr.*, 1898, No. 26.

3. Plumier: *Jour. de physiol. et de path., gén.*, 1904, vi, 655.

within the left auricle always fell, showing that the augmented contraction of the left heart could then cope effectively with the rise of systemic pressure. Similar results were even more recently obtained by Petitjean.<sup>4</sup>

Extensive as these researches are, they are incomplete, as far as the therapeutic use of adrenalin in hemoptysis is concerned. Experimentation with feeble doses, such as alone can be used in therapeutics, has been practically neglected. In the zeal to obtain decisive results in one direction or another, large doses were naturally used. One is not warranted in assuming from these results that the same changes occur when small doses are given during a hemorrhage. Small doses exert little slowing influence on the heart through the vagus. Besides, I have found that the irritability of the vagus center toward adrenalin diminishes with the progressive loss of blood, so that doses which slow the heart in normal animals fail to do so in bleeding ones. These considerations indicate that the use of therapeutic doses of adrenalin in internal hemorrhage does not cause a damming back of blood into the pulmonary circuit.

### III. CLASSIFICATION OF PULMONARY HEMORRHAGES

According as the blood from a ruptured pulmonary vessel reaches the exterior through the respiratory passages and mouth, or remains concealed within the lung parenchyma or pleural cavities, pulmonary hemorrhages may be clinically classified as *external* and *parenchymatous*. This classification is also of physiologic importance. In the first place, the anatomic relations of the pulmonary vessels are such that the larger trunks accompany the larger bronchi and grow smaller with them toward the external surface of the lungs. This arrangement determines that external hemorrhages, as a rule, come from larger vessels than those confined to the parenchymatous tissue. Secondly, the smooth surface of the bronchi, from which blood is continually removed by respiration when a vessel ruptures into them, compares unfavorably with the reticular coagulating surface supplied when a vessel ruptures into the parenchyma or through the parenchyma into the pleural cavities.

### IV. PARENCHYMATOUS HEMORRHAGES

It was the original intention to study the effect of adrenalin on both classes of hemorrhage. It was found, however, that when parenchymatous hemorrhages were created by the excision of a piece of lung tissue

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4. Petitjean: Jour. de physiol. et de path., 1908, x, 401.



with a laterally curved scissors, cessation occurred with remarkable rapidity. Visiting scientists, on seeing one of these profuse hemorrhages created during an experiment, unfailingly prophesied the animal's prompt death, but were as unfailingly astonished a few minutes later to see the hemorrhage entirely stopped without much change in blood pressure. In no case was the fall more than 8 mm. Evidently there is no form of medication which can improve on Nature's process in treating these hemorrhages. For this reason the research was limited to external hemorrhages.

#### V. EXTERNAL PULMONARY HEMORRHAGES (HEMOPTYSIS)

*Methods Employed.*—In attempting an experimental investigation of external hemorrhages, anatomic obstacles at once arose. The large pulmonary trunks divide into smaller and smaller vessels almost ex-

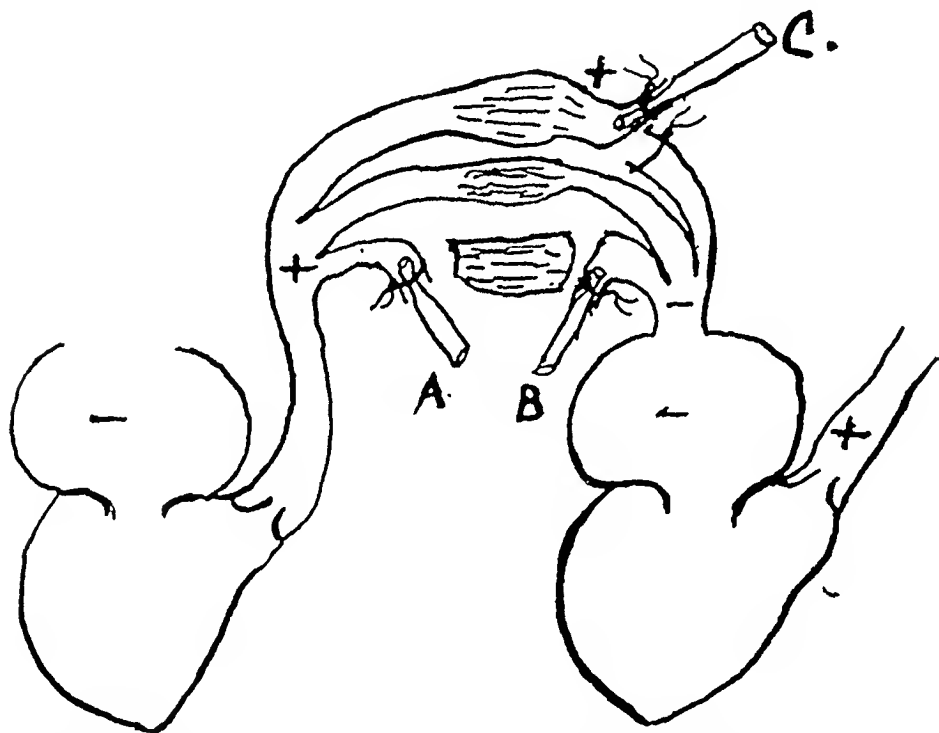


Fig. 1.—Diagram to show insertions of cannulas. A, cannula in central end of pulmonary artery; B, cannula in central end of vein to record pressure in left auricle; C, cannula in peripheral end of pulmonary vein. Plus and minus signs indicate the direction in which the volume of blood changes after administration of adrenalin.

clusively within the lung tissue. This made it impossible to isolate and cut a certain vessel at the most opportune time, as was done in studying intestinal hemorrhages. It was also found that there was no satisfactory way to measure the blood from a hemorrhage created by a hook introduced into the bronchi through a bronchoscope. Less direct proce-

dures were then resorted to, and it was determined to test the effect of adrenalin on the pressure and flow from the large pulmonary veins and arteries. The artery and vein entering the lower lobe of the left lung were reached by resection of the four lower ribs on the left side. By means of canulas inserted into the central end of the artery and connected with a mercury manometer, the pressure in the pulmonary arteries was recorded. By similar connection with the peripheral end of the vein the venous pressure was recorded, while the left auricular pressure was obtained by inserting a cannula into the central end of this vein (Fig. 1). To record the outflow from these cannulas, a rubber tube, 20 cm. long, was attached and the blood led to an apparatus which continually weighed and recorded the amount of blood. When all was ready the clamp on the vessel was removed, the flow recorded and small doses of adrenalin intravenously injected when desired.

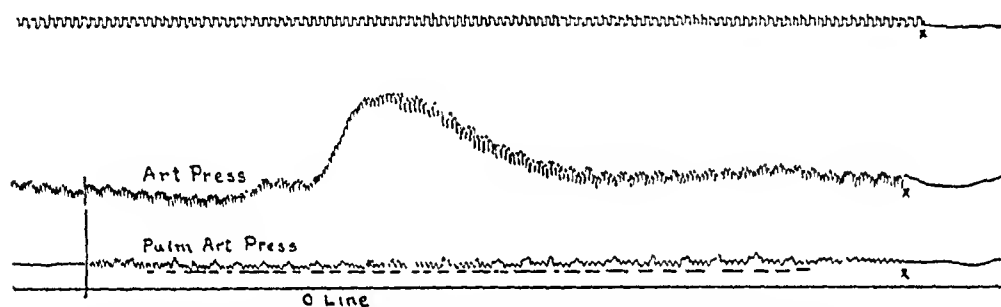


Fig. 2.—Segment of record taken Sept. 16, 1908. Effect of 0.025 mg. adrenalin on carotid and pulmonary arterial pressures.

*The Effect of Adrenalin on Pulmonary Arterial Hemorrhages.*—The effect of therapeutic doses of adrenalin on the pulmonary arterial pressure was tested in twenty-one experiments, the results of which are typified by the curve shown in Figure 2. Evidently such doses, though they cause a fair rise of systemic pressure, raise the pulmonary arterial pressure very little or not at all. Such results fail to give any evidence that adrenalin will cause an increase in pulmonary arterial hemorrhage.

Records of the outflow of blood from such vessels as are illustrated in Figure 3 invariably showed an increased bleeding after administration of adrenalin. This was not due to the variation of the animals to adrenalin, for in a number of cases outflow and pressure measurements were consecutively made on the same animal. In each case it appeared that adrenalin increased the outflow even when the pressure did not vary. This increase lasted while the pressure rose, but was never followed by a diminution or cessation, as in intestinal hemorrhage.

These experiments certainly indicate that hemorrhages from the pulmonary arteries are increased even by therapeutic doses of adrenalin. They also show that changes of pulmonary arterial pressure, as recorded by the mercury manometer, give no reliable indication of the quantity of blood present within the vessels, and that it is the volume of blood rather than the pressure which determines the amount of blood lost in pulmonary hemorrhages. This is probably so because the pulmonary

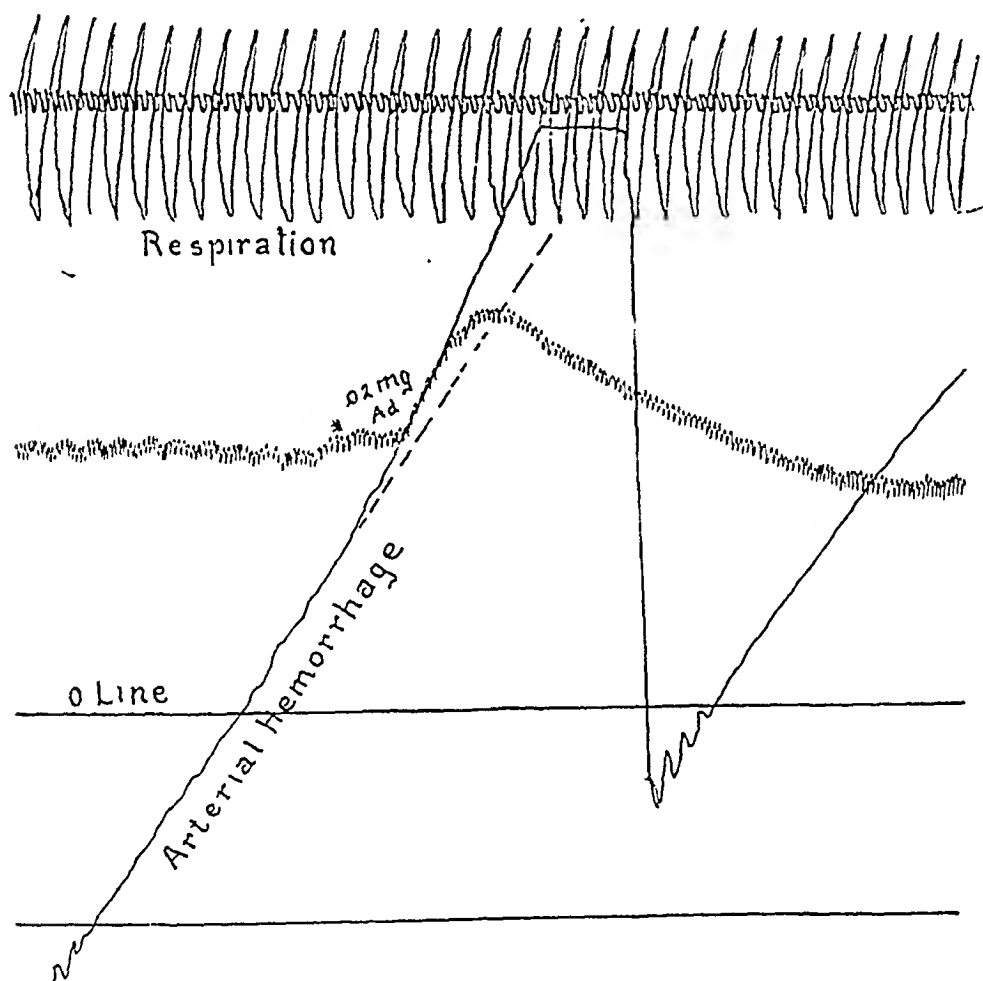


Fig. 3.—Segment of record from Experiment 80. Effect of 0.02 mg. of adrenalin on outflow from pulmonary artery.

vessels accommodate quite a quantity of blood without much change in pressure.

*The Effect of Adrenalin on Pulmonary Venous Hemorrhage.*—The left auricular pressure, as obtained from one pulmonary vein near its entrance (Fig. 1), has been taken by previous investigators to furnish

an index of pressure in the other pulmonary veins emptying into it. The results of my experiments entirely corroborated those of Plumier, in that a fall of left auricular pressure invariably resulted, in spite of a rise of systemic pressure (Fig. 4). This certainly indicates that a "back effect" from the systemic rise does not occur. It does not warrant the conclusion drawn by previous workers, that the venous pressure fell and that thus we had evidence of a constricting action of adrenalin in the pulmonary circuit, for, if a cannula was inserted into the peripheral end of one of the pulmonary veins, the pressure slightly rose there (Fig. 4). This indicates a greater transfer of blood from the pulmonary arteries to the veins.

Records of the quantity of blood flowing from these cannulas showed that adrenalin increased the flow from the peripheral end of a pulmonary vein (Fig. 5), even though the amount thrown out by the left auricle through the central end was less.

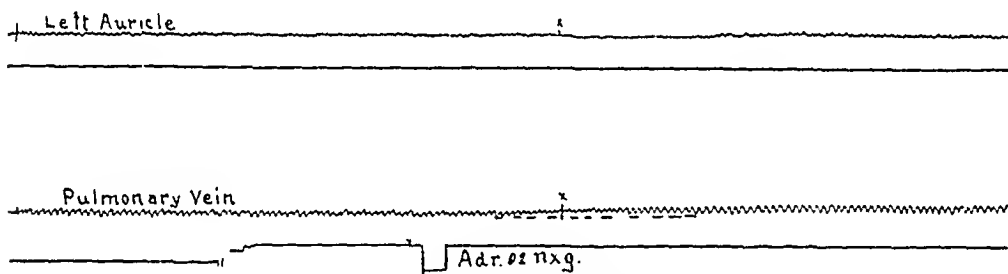


Fig. 4.—Segment of record showing effect of adrenalin (0.02 mg.) on pressure in left auricle and pulmonary veins.

These experiments indicate that adrenalin increases the quantity of blood in the pulmonary veins as well as in the arteries, and that its use in pulmonary hemorrhage can not be looked on as favorable.

As has been repeatedly emphasized, the accumulation of blood is *not due* to a damming back from the arterial side. The left ventricle, stimulated to more powerful contractions by adrenalin, is able to cope with the arterial rise as long as the heart is not perceptibly slowed. Plumier prefers to interpret the rise of pulmonary arterial pressure as a constriction of the pulmonary vessels, but this assumption is not in accord with the fact that the pulmonary venous pressure also rises and the out-flow increases. It seems that the augmented contractions of the right heart throw more blood into the pulmonary circuit, but that the left

heart receives only a fraction of this increase, because blood is accommodated more readily by the distensible pulmonary vessels than it is forced ahead.

## VI. CONCLUSIONS

1. Small doses of adrenalin that do not slow the heart generally cause no rise of pulmonary venous and arterial pressures, or only a feeble rise, even though the systemic pressure rise appreciably.
2. Pressure measurements, however, give no accurate estimate of the

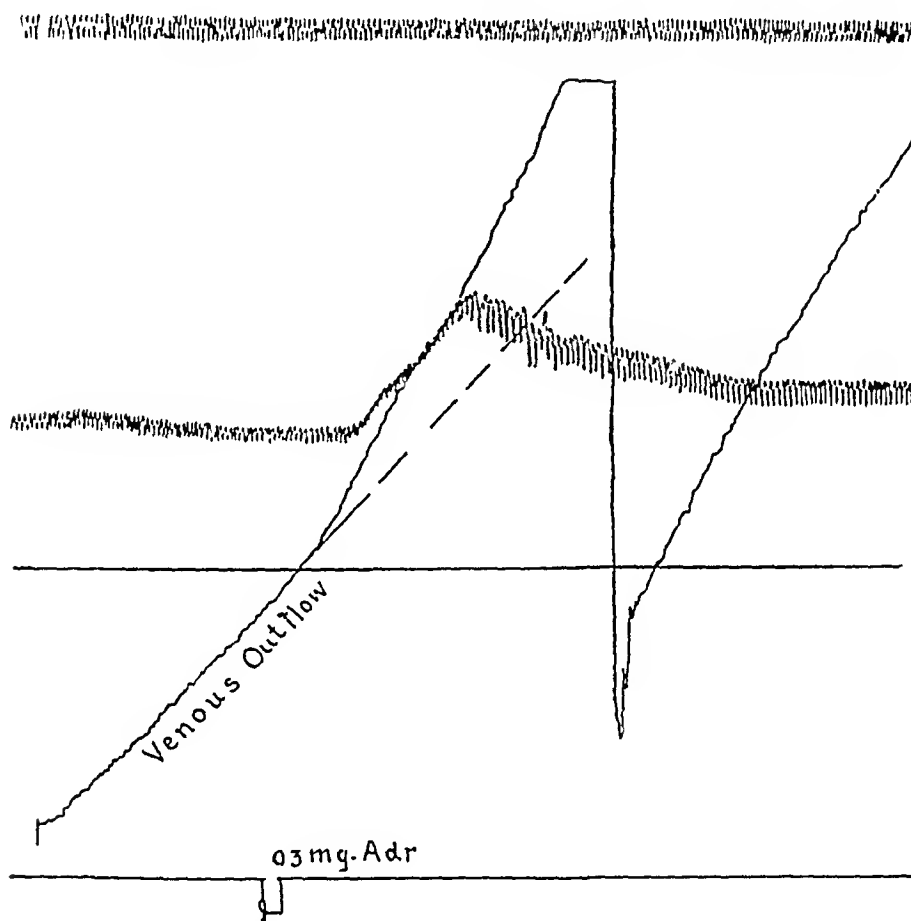


Fig. 5.—Segment of record showing effect of adrenalin (0.03 mg.) on outflow from peripheral end of pulmonary vein.

blood content of these vessels, for outflow records show that this is decidedly increased by adrenalin.

3. This increase is not due to a "back effect" from the systemic rise, for the pressure in the left auricle falls. It is not due to a constriction of the pulmonary vessels, for the venous pressure should then fall and not rise. It is probably due to the fact that the total volume of blood

thrown out by the augmented contraction of the right ventricle is not entirely forced ahead to be utilized in the feeding of the left heart, but, instead, is stored in the distensible pulmonary vessels.

4. Adrenalin is not a satisfactory drug to use during pulmonary hemorrhage to raise the general blood pressure. Further researches are required to determine how it compares with other modes of treatment.

619 Church Street.

# ARTIFICIAL RESPIRATION IN THE TREATMENT OF EDEMA OF THE LUNGS

A SUGGESTION BASED ON ANIMAL EXPERIMENTATION \*

HAVEN EMERSON, A.M., M.D.

NEW YORK

On three separate occasions, in 1906, 1907 and 1908, while demonstrating the effects of extreme peripheral resistance on the heart and pulmonary circulation, I have noticed a definite result of artificial respiration when administered to an animal apparently dying from acute pulmonary edema.

The physical causes of the benefit apparently derived from this procedure seem to agree so well with facts already accepted in physiology, and the possibility of application of the method in certain kinds of clinical cases seems so reasonable, that I offer this communication in the hope that practical tests may, before long, be sufficiently conclusive to establish its value therapeutically, or to relegate it to the mass of theories that have failed.

It will save time if I call attention to a few points regarding the effect of respiration on the circulation. The respiratory fluctuations in blood pressure which any one can appreciate in the radial pulse are due to the variation in the ease of passage of blood between the right and left side of the heart and to the inherent elasticity of the lungs. The expansion of the lungs allows a wider path for the blood and an increase in the blood in the pulmonary vessels, and at the same moment a diminished resistance to the passage of the blood through the lungs, a lessened burden for the right ventricle. When the lungs collapse in expiration, the elastic recoil empties the pulmonary vessels, and at the same time narrows the path through which the right ventricle must now pump the blood. So we find in the last two-thirds of inspiration and the first third of expiration a rising pressure, the remainder of the respiratory cycle showing a falling pressure.

If we watch the results of positive pressure respiration properly applied, we notice an entire reversal of the blood pressure changes above described. During the inspiratory phase, which is due to the forcing of

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\*From the Department of Physiology of the College of Physicians and Surgeons of Columbia University in the City of New York. Read at the meeting of the Section on Medicine of the New York Academy of Medicine, March 16, 1909.

air into the lungs under positive pressure, the normal conditions in the chest and in the pulmonary spaces are altered. The positive pressure exerted on the vessels in the lungs tends to empty them, or at least to obstruct their lumen, by just the amount of pressure exerted. The small vessels are squeezed, as it were, against the resistant pulmonary tissue, by air forced into the terminal vesicles through the trachea. During the expiratory phase the release from positive pressure permits a filling of the vessels again and a diminished resistance to the passage of blood from the right to the left heart. So it will be found that during positive pressure respiration, the so-called artificial respiration of laboratory procedure, the blood pressure falls during inspiration and rises during expiration.

For our present purposes the important thing to bear in mind is that rhythmical variation of pressure, applied at any point of the circulation, will serve to assist in the onward movement of the blood, and will in proportion to its extent assist the action of the heart. It has been found possible to continue a circulation of the blood simply by artificial respiration in an animal in which the heart is no longer capable of contracting, the valves allowing an onward movement with each inspiratory phase and preventing any regurgitation to fill the vessels during expiration.

If we modify the procedure of Professor Leo Loeb, who first called my attention to the use of adrenalin to cause edema of the lungs, we can develop gradually an acute cardiac insufficiency. Massive and repeated doses of adrenalin given intravenously in a cat will produce acute dilatation of the left ventricle, due to sudden and extreme constriction of all the systemic arteries. The dilatation of the left ventricle allows of a mitral regurgitation, an acute congestion of the lungs and a dilatation and failure of the right heart. The inability of the right ventricle to force the blood received from the auricle against the back pressure of blood regurgitating from the left auricle allows of increase in the stagnation of the pulmonary circulation. Edema—that is, a collection of blood serum in the air spaces of the lungs—occurs, increasing until pink or clear serous frothy fluid appears in the trachea. Respiratory movements become exaggerated and later feeble and spasmodic, and the animal will presently die of asphyxia due to a flooding of the air spaces of the lungs by blood serum.

If, when we find respiration showing definite signs of beginning asphyxia, when the veins are becoming distended and deepened in color, cardiac insufficiency is established and the incompetency is increasing, and when we can hear moist râles over the lungs, and when we know that



cardiac insufficiency is established and the incompetency is increasing, we then apply artificial respiration, through the tracheotomy tube, gently distending the lungs and allowing them to collapse with or without suction, we shall find presently an amelioration in the animal's condition. The full expansion of the lungs, due to distention from within, forces a considerable amount of blood onward to the left auricle, and as the respiratory phase extends over two or three heart beats, an increased amount of blood will have passed the mitral valve and there will be more room in the pulmonary vessels when expiration occurs for the blood held in the distended right ventricle, and a diminished resistance in the lungs against which the right ventricle can now successfully empty itself.

This at least seems the probable explanation for the improvement in the circulation which presently occurs. The lungs appear free from moist râles, the heart beats more vigorously, the distention of right and left side diminishes and when the artificial respiration is discontinued after about half an hour the animal is able to breathe normally and shows none of the signs of insufficient circulation or respiration. The effect of the adrenalin has worn off, the heart muscle has recovered from its acute overloading, the pulmonary circuit is no longer engorged with regurgitated blood, and to all intents and purposes the heart and lungs are again performing their functions normally.

The bearing of this purely experimental procedure on the individual case of edema of the lungs in the human subject may not appear quite clear, and I shall try to point out the conditions in which I believe this lesson can be applied with advantage.

In many instances a hypertrophied and properly compensating heart, which has adjusted itself gradually to a valvular defect or to an increasing inelasticity of the arteries or persistent increase of peripheral resistance from any one of a number of causes, will, if a sudden strain is put on it, develop an acute incompetence. Overexertion physically, over-indulgence in food or wine, excess of psychical excitement or an unfortunate combination of all three, or an attack of contracted arteries or bronchi may be the determining factor. With a heart just able to maintain its competence under favorable conditions, even if it is not the seat of myocardial degeneration, insufficiency is easily precipitated and pulmonary edema is likely to be developed unless the failing heart action is of very brief duration. Under such conditions as I have above described, I believe it would be a valuable aid to the necessary medication if artificial respiratory movements were used. With the patient in the semirecumbent position, which is usually assumed when cardiac dyspnea

is marked, raising the arms above the head and then pressing them against the sides of the thorax or, better, across the upper part of the abdomen, ought to establish the accessory pumping action which, under normal conditions, facilitates the flow of blood through the lungs, but which the patient, in his enfeebled condition, is unable to do for himself. This assistance, I believe, should prove more prompt and effective than any medication, and would at least be giving mechanical relief to the overloaded heart muscle, while arterial relaxation and cardiac stimulation are being accomplished by drugs. I think such treatment would be indicated whenever the edema and cardiac incompetence are of sudden development and are due to causes which are likely to prove of brief duration or can be removed by appropriate treatment. Edema, when due to cardiac failure in the course of pneumonia or appearing as the inevitable terminal feature of a chronic endocarditis, could not be expected to respond to such temporary relief as artificial respiration would offer. Moreover, I hope I shall not be misunderstood as advocating forced respiration by intubation or tracheotomy, for I certainly think such measures would be quite unjustifiable. My belief, based on experimental observations, is that artificial respiratory movements, directed to establishing a rhythmical expansion and contraction of the thorax, are worthy of clinical trial in cases of acute cardiac insufficiency accompanied by edema of the lungs.

120 East Sixty-second Street.

# PULMONARY EDEMA TREATED BY ARTIFICIAL RESPIRATION

REPORT OF A CASE \*

THEODORE B. BARRINGER, JR., M.D.  
NEW YORK

Several weeks after seeing Dr. Emerson's experiment, in the spring of 1908, and realizing the lesson it taught in clinical therapeutics, I was called to one of my patients, whom I found in an attack of acute cardiac insufficiency. A report of this case follows:

*History.*—The patient, a housewife, aged 47, multipara, had had scarlet fever and chorea when a child, and a severe attack of inflammatory rheumatism in 1895. She had had dyspnea on exertion for the last three or four years, and five or six attacks of cardiac insufficiency during this time. The chief symptoms were rapid heart action, dyspnea, cyanosis and occasionally hemoptysis. None of them was severe, and they lasted, as a rule, not over four or five hours.

*Examination.*—The patient was 5 feet 4 inches tall and weighed 150 pounds. The apex of the heart was in the fifth space,  $4\frac{1}{2}$  inches out; there was a marked right heart hypertrophy, and at the apex a loud presystolic crescendo murmur and a faint systolic murmur transmitted to the left. The lungs were negative; the urine negative, except for an occasional hyaline cast. At the time of my emergency call I found the patient sitting up in bed, cyanosed, very dyspneic and restless, with a tracheal rattle and a pulse 132 to the minute, quite irregular and of low tension. The heart showed a diastolic rumble instead of the usual presystolic crescendo murmur. The lungs showed quantities of moist râles which extended as high as the third or fourth ribs in front.

*Treatment.*—My patient evidently was suffering from an auricular paralysis. I opened the window, put an inverted chair with a pillow on it behind her back and gave her hypodermic injections of tincture of digitalis, strychnin and morphin. Then, with the husband's aid, I carried out artificial respiration. We raised and lowered the arms slowly ten or twelve times, then stopped for a few moments, because it tired the patient, and then resumed the movements. After a few arm movements she coughed and raised several large mouthfuls of pink, frothy sputum, and this expectoration was repeated a number of times. Between the periods of artificial respiration the tracheal rattle would continue and nothing would be expectorated. At the end of an hour the artificial respiration was stopped and the hypodermic stimulation repeated. The rattling in the throat had now ceased, the moist râles in the lungs had become much less numerous and the pulse was 118 per minute.

In two or three days the patient had entirely recovered.

The cause of the cardiac insufficiency and pulmonary edema in this case was, of course, different from that in Dr. Emerson's animal experi-

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\*Read at a meeting of the Section on Medicine of the New York Academy of Medicine, March 16, 1909.

ments. The pathology of acute cardiac failures in these cases of mitral valve lesions is probably as follows: Some overexertion, mental or physical, interferes with what Mackenzie calls the tonicity of the right ventricle, and it dilates; tricuspid regurgitation ensues; the right auricle dilates and auricular paralysis follows. The right-heart failure is evinced clinically by the marked cyanosis, the dyspnea, the irregular rhythm, and the pulmonary edema.

My patient would very possibly have recovered if nothing had been done for her, although this was the severest attack she had ever had. The hypodermic stimulation was naturally of much help to the right heart, but I feel that the artificial respiration also aided very materially the pulmonary circulation in the way Dr. Emerson has described. Certainly the lungs were relieved of much of the transudate. This was one of the few times I have seen the typical sputum of pulmonary edema as described in the text-books.

It is interesting to note what Mackenzie says, in his recent book on diseases of the heart, about the treatment of pulmonary edema:

When, however, the right ventricle is enfeebled, the assistance of the respiratory movements becomes necessary. An important part can be played, in suitable cases, by placing the patient in a position to breathe freely, avoiding the restraint exerted by pressure on the ribs, and by making the patient inspire deeply.

In the Presbyterian Hospital (New York) Medical and Surgical Report for 1897, Norton reported a case of carbolic-acid poisoning treated with the Fell-O'Dwyer forced respiration apparatus. The pulmonary edema which ensued was cleared up rapidly by the artificial respiration. In this case the pulmonary circulation was aided by a rhythmical positive pressure, instead of by a rhythmical negative pressure, as in my case.

34 West Eighty-fourth Street.



# A REPORT ON THE EXPERIMENTAL PRODUCTION OF CHRONIC NEPHRITIS IN ANIMALS BY THE USE OF URANIUM NITRATE.\*

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SAN FRANCISCO.

## INTRODUCTION.

The study of chronic nephritis is one which for many years has commanded the interest and investigation of many observers. Since 1827, when Richard Bright first described the condition which we now know as Bright's disease, many attempts have been made to determine the relationship existing between the various types of diseases of the kidney, and the conditions which influence the development of those different types. It is impossible to discuss here the immense amount of literature which has been written on this subject, or to consider the bitter controversies which have waged. Even to-day, although certain types of subacute and chronic conditions are universally recognized, there is great difference of opinion as to the etiologic factors at work in the development of each.

In 1879 Weigert<sup>1</sup> published an elaborate discussion of kidney diseases viewed from the standpoint of pathologic anatomy, and in his classification he described a series of kidneys as "chronic hemorrhagic with heart hypertrophy" in which there are definite interstitial changes associated with the parenchymatous degenerations. This group he subdivides into three smaller groups:

1. Those kidneys which are normal or slightly larger than normal in size, are red or mottled in color and are firmer in consistency than normal. The capsule strips easily, the cut surface bulges a little on section, and the cortex is pale or mottled in color, while the pyramids are darker. There is a certain amount of fatty degeneration of the epithelium of the convoluted tubules, many of which are more or less completely obliterated while others are dilated and contain a clear or

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\* From the Pathological Laboratory of the University of Toronto, Canada.

\* A preliminary report of these experiments was read before the Association of American Pathologists in Washington, D. C., in June, 1907, and before the Laboratory Section of the Canadian Medical Association in Montreal, P. Q., in August, 1907.

1. Weigert: Die Bright'sche Nierenkrankungen von pathologisch-anatomischen Standpunkte. Samml. klin. Vortr. (Volkmann's), 1879, clxii-clxiii. 1411.

granular exudate in their lumens. The collecting tubules and the loops of Henle contain casts. The glomeruli may be unchanged or may show thickening of the capsules, and there may be connective tissue change in the tufts. There is some proliferation of the intertubular connective tissue, and there may or may not be thickening of the intima of the arteries.

2. Forms which are similar to those just described, but which show in addition definite macroscopic granulations on the surface. There is greater glomerular and tubular change and much more new growth of connective tissue. Clinically this type contrasts with the chronic interstitial, in its shorter duration, the greater amount of albumen, and the presence of edema. It may be considered as a further stage in the process of which the type last described forms a part.

3. Large white kidneys which closely resemble the above type both clinically and histologically except that they are anemic and show much more fatty change.

Weigert also refers to kidneys which are atrophied and granular, with very marked degeneration of the glomeruli and tubules, with the formation of cysts and with calcium deposit, and with marked diffuse increase of the connective tissue. This group he divides into two smaller groups: (a) the small red atrophic kidney; (b) the small white atrophic kidney. The condition is characterized clinically by the long duration, the absence of edema, and the hypertrophy of the left ventricle of the heart.

In discussing the etiology of chronic nephritis he points out that a parenchymatous nephritis, i. e., one in which the parenchymatous change is the most marked but which shows also some interstitial change, can pass over into the stage of a shrunken kidney. He also believes that all new formation of connective tissue in the kidney is invariably preceded by degeneration of the tubules or glomeruli.

In 1897 Senator<sup>2</sup> made a definite division of contracted kidneys into two groups, primary and secondary. The primary sclerotic, together with the arteriosclerotic, form by far the greater number of cases of chronic nephritis, and are progressive from the beginning without any primary acute inflammation, and often without acute exacerbations. The secondary contracted kidney on the other hand, dates from some acute infection, and has an initial acute stage which may be considered as a true parenchymatous nephritis. He believes

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2. Senator: Die Pathogenese der chronischen Nephritis. Berl. klin. Wehnschr., 1897, xxxiv, 820.

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that this type is also progressive because of some disturbance of the vascular system.

Samuel West<sup>3</sup> in his Lettsonian Lectures in 1899 admits that viewed from a pathologic standpoint there is a possibility of a progression from an acute parenchymatous inflammation through the stages of the subacute to the small granular or atrophic kidney; but believes that such a process is practically never found clinically. He believes it as reasonable to suppose that the so-called primary parenchymatous nephritis is an acute exacerbation of a pre-existing chronic condition, as that it is the initial lesion upon which the subsequent granular condition depends.

Friedrich Müller<sup>4</sup> in 1904 points out that acute parenchymatous nephritis due to many infections may eventually go on to the development of a contracted or indurated kidney. He believes that many of the so-called idiopathic or primary indurated kidneys are thus classified because a sufficiently careful search for a definite causative factor has not been made. He believes that while in many cases of nephritis following acute infection there may be a long-drawn-out and progressive condition with slight disturbances of temperature and with periodic exacerbations, yet in a certain number of such cases there is a complete cessation of all symptoms and freedom from any disturbance for many years. In such cases he considers that the condition is that of healing by scar formation, and that it is not progressive, although a kidney so damaged must necessarily offer a focus of lowered resistance to subsequent insult. He compares the lesion to that found in the endocardium after a healed valvular endocarditis, or to that condition of fibrosis which is found in the lung after an unresolved pneumonia. Although the clinical course of this type differs from that of the so-called idiopathic chronic nephritis in the acute onset with the presence of albumen and casts, and in the gradual clearing up of the acute symptoms with the subsequent development of polyuria and hypertrophy of the left ventricle, yet histologically the kidneys can not be distinguished from one another.

In 1906 Lohlein<sup>5</sup> showed that in a certain number of patients who succumbed to chronic nephritis there was a definite history of a pre-

3. West: Some clinical aspects of granular kidney. *Brit. Med. Jour.*, 1899, i, 329.

4. Müller: Morbus Brightii (Korreferat). *Verhandl. d. deutsch. path. Gesellsch.*, 1905, ix, 64.

5. Lohlein: Ueber die entzündlichen Veränderungen der Glomeruli der menschlichen Nieren und ihre Bedeutung für die Nephritis. *Verhandl. d. deutsch. path. Gesellsch.*, 1906, 217.



existing infection followed by a quiescent period of several years before the appearance of the terminal symptoms. He based his conclusions on a study of scarlatina and diphtheria in which he found that glomerular change played a very important part in the nephritis following these diseases. He says that advanced fibrosis with hyaline change of the tufts and thickening of the capsules of the glomeruli may undoubtedly date back to a glomerular nephritis in a certain number of young subjects in which the history definitely locates the primary attack and excludes probability of subsequent irritation to the kidneys.



Fig. 1.—Guinea-pig 25: 46 injections of 0.25 mg. in 77 days. Dilatation of tubules in the medullary rays, cellular infiltration between tubules, desquamated cells in the dilated lumens, and glomerulus with thickened capsule surrounded by round-cell infiltration.

In view of such differences of opinion resulting from purely clinical observations, an attempt has been made to produce a chronic nephritis in animals by experimental means, in the hope that some condition might be produced analogous to that found in man, and that from the method of experimental production some light might be thrown on the etiologic process which produces the condition in

man. Uranium nitrate was the irritant selected, because Richter<sup>6</sup> has recently shown that by the use of this drug "it has become possible to produce a diseased condition in animals which is analogous throughout to Bright's disease." The experiments were performed in the Pathological Laboratory of the University of Toronto, under the direction of Professor J. J. MacKenzie. I wish here to express my gratitude to Professor MacKenzie for the interest with which he has followed the work, and for the many helpful suggestions he was at all times ready to give. I am also indebted to Dr. V. E. Henderson for help and advice throughout the course of the experiments.

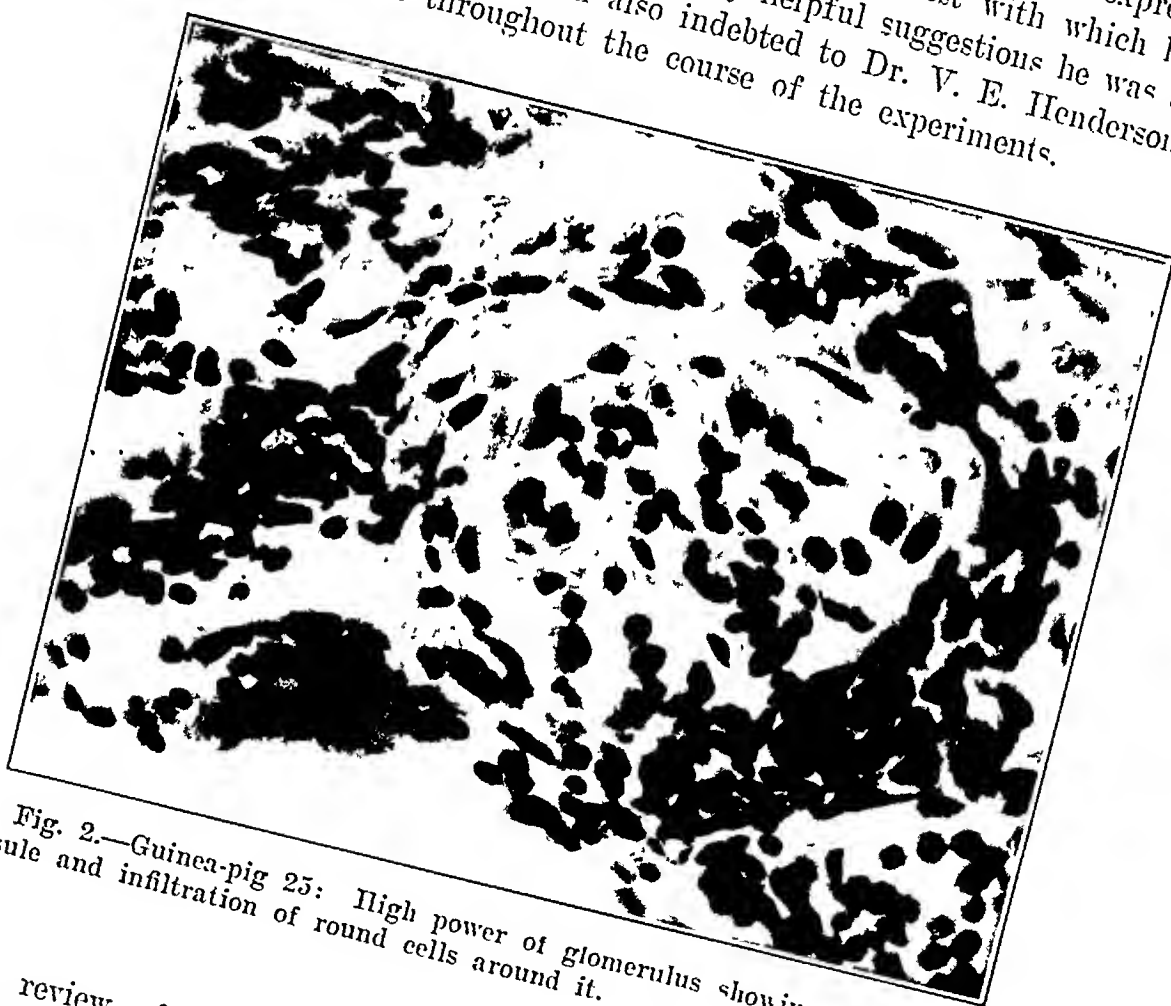


Fig. 2.—Guinea-pig 25: High power of glomerulus showing thickening of capsule and infiltration of round cells around it.

#### HISTORICAL.

A review of the literature on experimentally produced chronic nephritis forces one to the conclusion that the results obtained have not been very satisfactory. In 1904 Rose Bradford<sup>7</sup> suggested that

6. Richter: Die experimentelle Erzeugung von Hydrops bei Nephritis. Beitr. z. klin. Med. Festschr. Herrn. Prof. Senator. Berlin, 1904, 283. Ex-perimentelle über der Nierenwassersucht. Berl. klin. Wehnschr., 1905, xlii, 384.
7. Bradford: On Bright's disease and its varieties. Croonian Lectures, 1904. Lancet, London, 1904, clxvii, 191.

a possible explanation of the many failures might lie in the fact that up to that time no irritant was known by which one could produce in animals a condition analogous to acute Bright's disease in man, i. e., an acute parenchymatous nephritis associated with the formation of edema. An exhaustive review of the literature up to January, 1907, may be found in Lyon's report<sup>8</sup> entitled, "An Experimental Study on the Action of some Poisons and Toxins on the Kidney and Spleen," and in Ophüls' article<sup>9</sup> on "Experimental Chronic Nephritis." Space will not permit more than a very brief review at this time.

Bradford<sup>7</sup> has stated that mere destruction of renal parenchyma by a metallic poison is not sufficient to lead to the production of a true

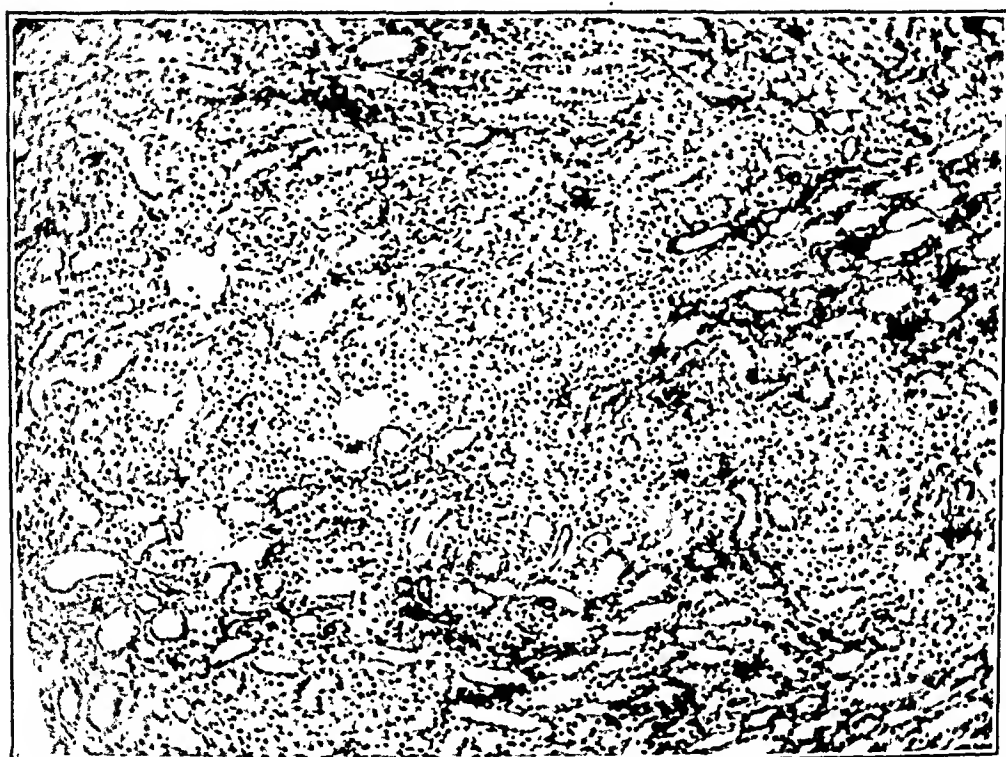
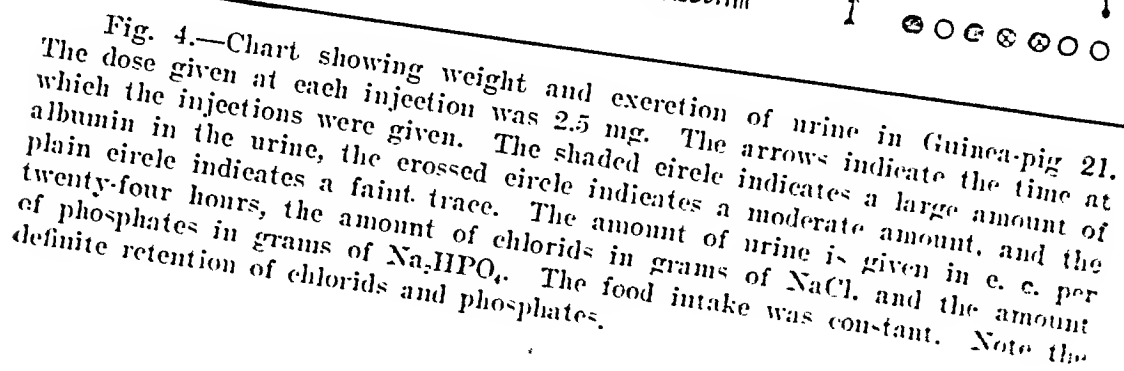


Fig. 3.—Guinea-pig 26: 36 injections of 0.25 mg. in 45 days. Very low power showing the wide distribution of the dilated tubules and the cellular infiltration between them.

contracted kidney. Potassium bichromate injected directly into the kidney of an animal through the renal vein causes an extensive destruction of the renal epithelium, and if the animal survives the first acute attack, a subsequent atrophy of the tubules and glomeruli with

8. Lyon: Experimental study on the action of some poisons and toxins on the kidney. *Jour. Path. and Bacteriol.*, 1903-04, ix, 400.

9. Ophüls (W.): Experimental chronic nephritis. *Jour. Am. Med. Assn.*, 1907, xlviii, 483.



definite shrinking of the kidney. But the condition has not the picture of a true contracted kidney because there is no proliferation of connective tissue.

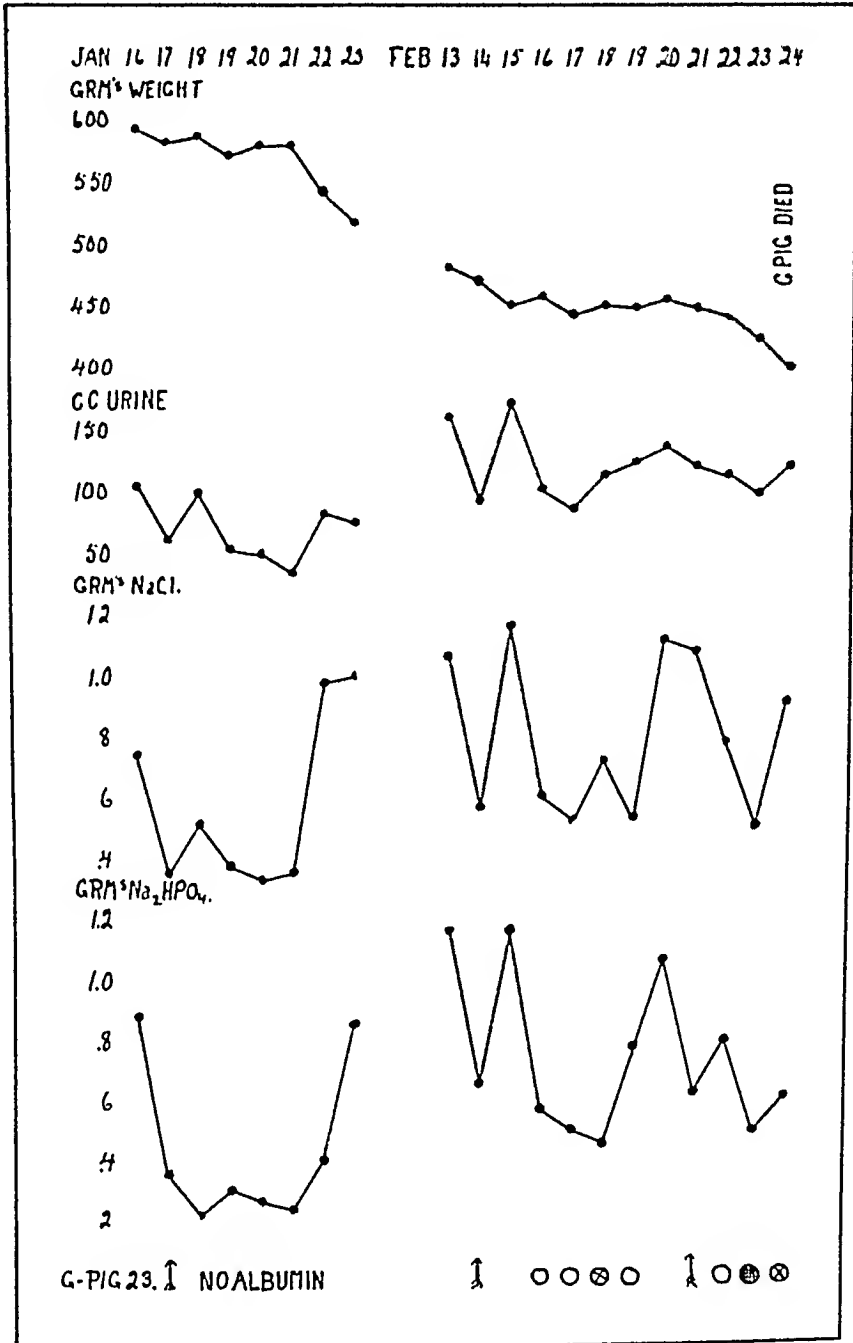


Fig. 5.—Guinea-pig 21: 6 injections of 2.5 mg. during 77 days. Glomeruli with thickened capsules and beginning proliferation of the endothelium, extreme atrophy of the tubules, and marked proliferation of the inter-tubular connective tissue.

Lyon<sup>s</sup> conducted an extensive series of experiments in which he produced acute nephritis in animals by the use of different poisons

and toxins. But in so far as the production of anything like a chronic condition was concerned his results were not very satisfactory. He succeeded in obtaining some new formation of connective tissue around some of the large deposits of calcium which occurred in the medulla of kidneys poisoned with corrosive sublimate, but he was unable to find any atrophied glomeruli with fibrous thickening of the capsule even in rabbits that had undergone a chronic poisoning which extended over a period of one hundred and ten days. In his summary he says: "In no case and by no variation of experimental method have I been able to produce and follow the evolution of changes at

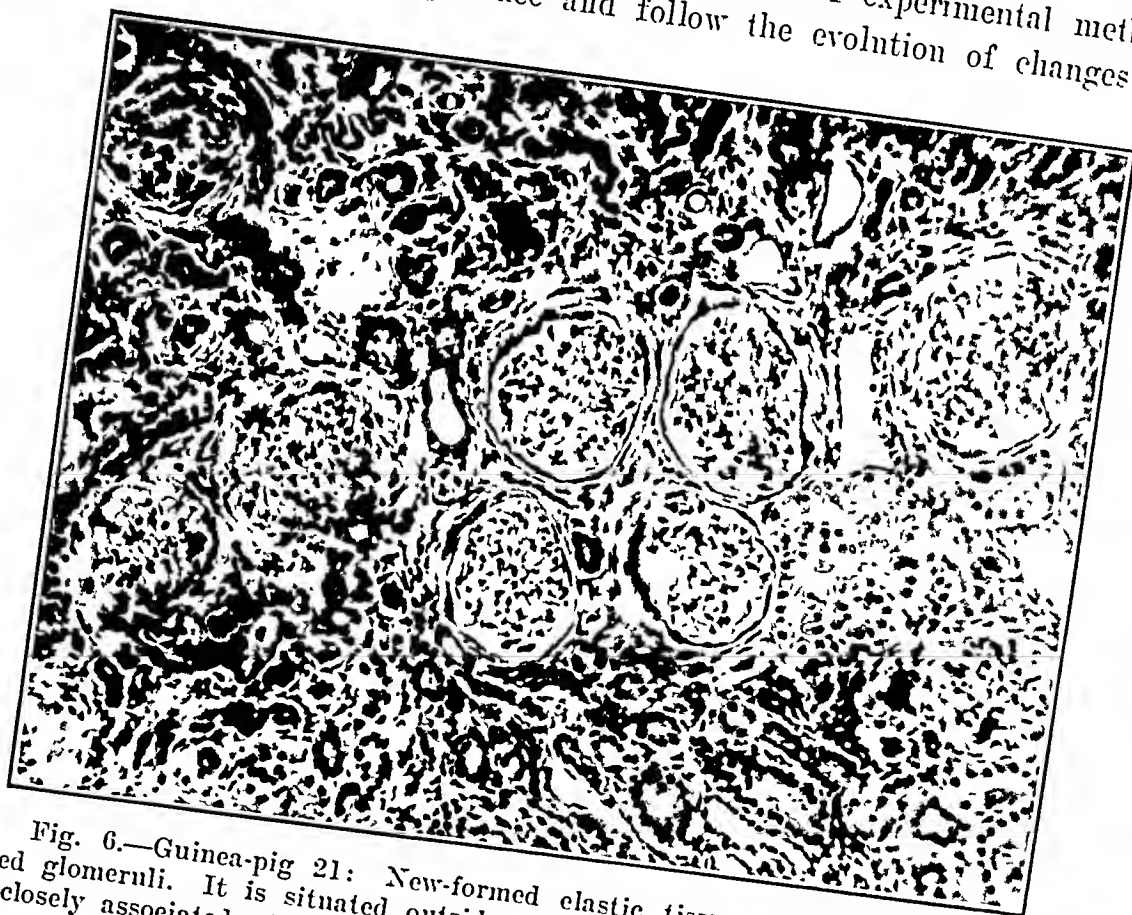


Fig. 6.—Guinea-pig 21: New-formed elastic tissue around slightly damaged glomeruli. It is situated outside the thickened basement membrane and is closely associated with the small artery. (Weigert's elastic tissue stain.)

all analogous to those which we find in sub-acute and chronic diffuse nephritis in man."

Petroff<sup>10</sup> in his experiments on the effects of various metals on the kidneys, found that when the action of the irritant was continued for a considerable length of time, there resulted necrosis of the renal

10. Petroff: Ueber die Einwirkung der Metalle auf die Nieren. Diss., Würzburg, 1905.

epithelium with definite proliferation of connective tissue. But at no stage of the experiments did he find albumin or casts in the urine.

Ehrlich<sup>11</sup> and Levaditi<sup>12</sup> were somewhat more successful, for by the use of vinyl amine they were able to produce a definite fibrosis of the kidneys in white mice, which was secondary to localized hemorrhagic necrosis of the papillae. This condition in one case was associated with characteristic urinary findings, as well as with hypertrophy of the left ventricle of the heart and albuminuric retinitis.

Pässler and Heineke<sup>13</sup> have recently reported a series of experiments by which they simulated the local conditions of chronic neph-

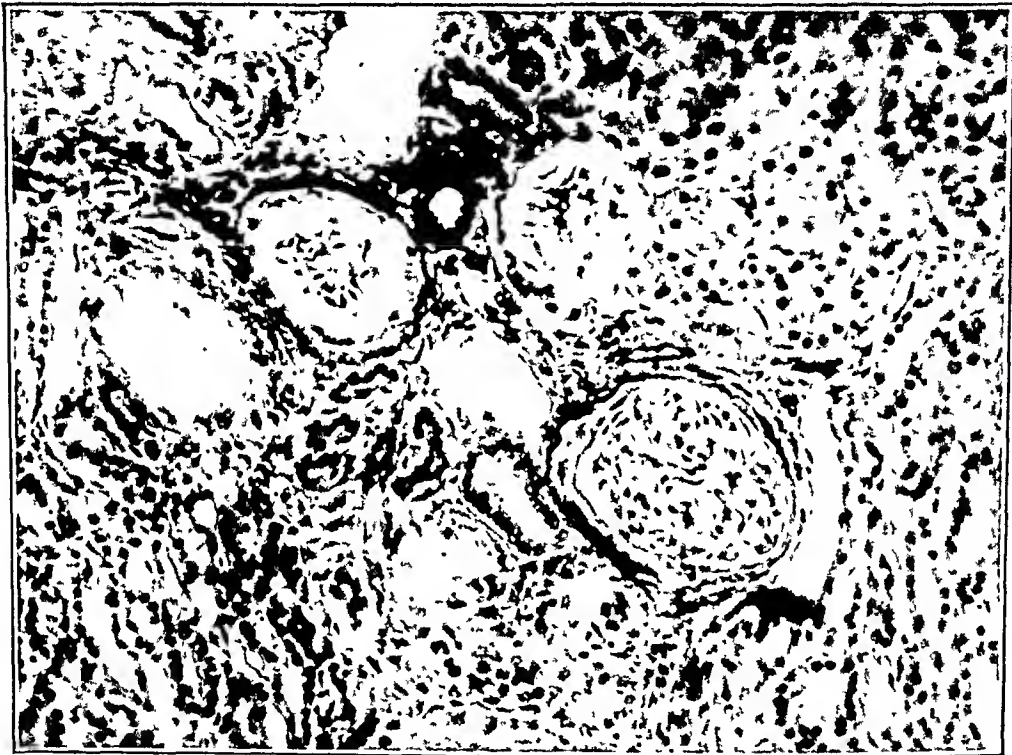


Fig. 7.—Chart showing weight and excretion of urine in Guinea-pig 23. Note the definite retention of chlorids and phosphates and the increased amount of urine excreted in the latter part. For full explanation, see legend of Figure 4.

ritis by directly destroying the greater part of the parenchyma of one kidney, and subsequently excising the other kidney. In certain animals

11. Ehrlich: Ueber die Zusammenhang von chemischer Constitution und Wirkung. 1898.

12. Levaditi: Experimentelle Untersuchungen über die Necrose der Nierenpapillae. Arch. internat. de Pharmacod., 1901, viii, 45.

13. Pässler and Heineke: Versuche zur Pathologie der Morbus Brightii. Verhandl. d. deutsch. path. Gesellsch., 1905, ix, 99.

which survived there resulted polyuria and hypertrophy of the left ventricle, and associated with this was the peculiar cachectic condition of chronic nephritis.

Ophüls<sup>9</sup> reports the production of sclerosis of the kidneys by feeding carbonate and acetate of lead in small doses to guinea-pigs and dogs respectively. The condition was associated with a typical lead anemia, but his observations correspond with those of Petroff in that he did not at any time find albumin or casts in the urine. In a more recent article<sup>14</sup> he reports a series of experiments on dogs and

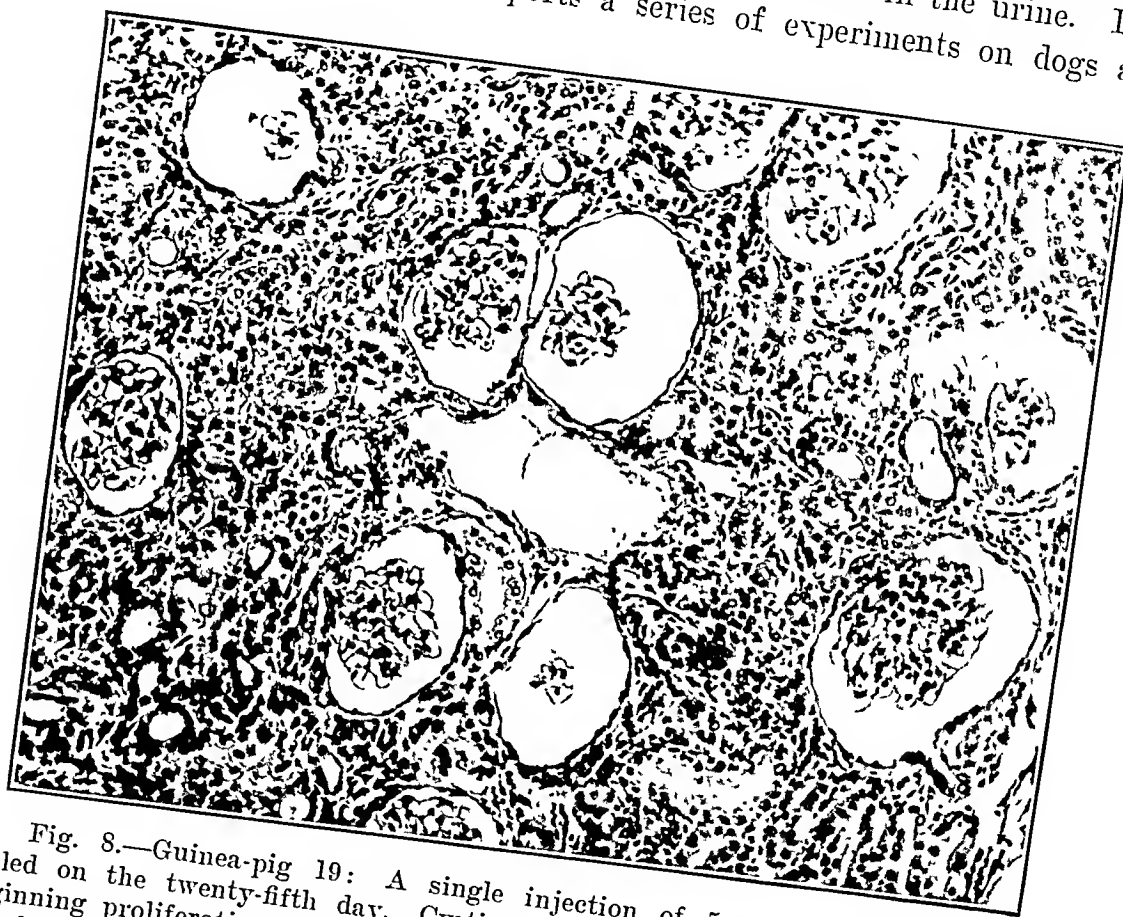


Fig. 8.—Guinea-pig 19: A single injection of 5 mg. The animal was killed on the twenty-fifth day. Cystic dilatation of the glomerular capsules, beginning proliferation of the interstitial tissue, and beginning atrophy of the tubules.

rabbits with potassium bichromate. By repeated subcutaneous injections he was able to produce definite foci of interstitial change, though he found that the kidneys had a strong tendency to recuperate even after severe subacute parenchymatous nephritis. In this series of experiments albumin and casts were found in the urine.

14. Ophüls (W.): Some interesting points in regard to experimental chronic nephritis. *Jour. Med. Research*, 1908, xviii, 497.



Haven Emerson<sup>15</sup> has found that repeated inhalations of ether, alcohol, amyl nitrite and chloroform produced varying degrees of chronic nephritis in dogs, and that in certain cases the manner of death of the animals would indicate that "the condition of the kidneys was probably responsible for their deaths." He also found that intra-renal injections of alcohol, and intramuscular injections of the acetate of lead produced chronic lesions in the kidneys, and that simple punctures into the kidney substance were followed by new growth of connective tissue along the line of puncture which, however, did not extend out into the surrounding kidney substance.

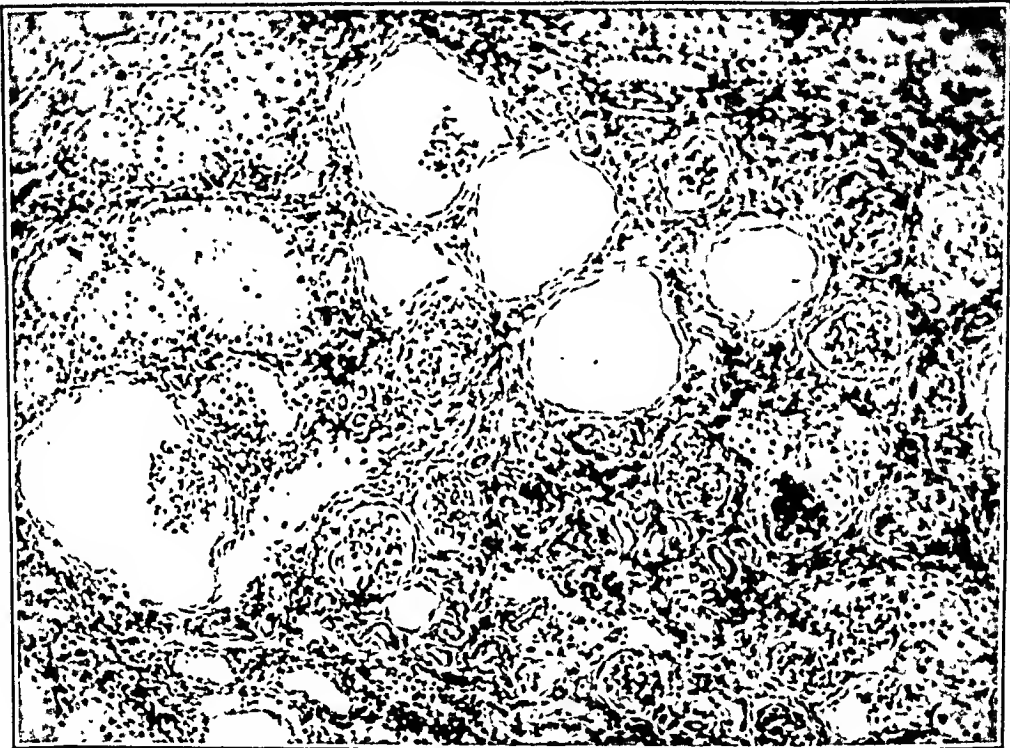


Fig. 9.—Guinea-pig 33: A single injection of 5 mg. The animal was killed in 117 days. Low power showing marked cystic dilatation of the glomerular capsules, and advanced fibrosis with atrophy of the tubules and thickening of the glomerular capsules. The low power will give some idea of the wide distribution of the fibrotic change.

Leopold<sup>16</sup> has reported the occurrence of an incipient fibrosis in the kidney of a dog which had been subjected to prolonged administra-

15. Haven (Emerson): An experimental and critical study of the etiology of chronic nephritis. *THE ARCHIVES OF INT. MED.*, 1908, i, 485.

16. Leopold: Ueber der Einwirkung von Salzen auf die Nieren (im Tierexperiment). *Ztschr. f. klin. Med.*, 1906, lx, 490.

tion of sodium chlorid; and recently Siegel<sup>17</sup> has referred to a condition found in a dog thirty days after acute poisoning with uranium nitrate which he describes as a chronic parenchymatous nephritis.

#### EXPERIMENTAL METHOD.

The animals taken for experiment were well grown guinea-pigs which weighed between 550 and 700 gm. They were fed on carrots and hay, except when under special observation in metabolism cages, when they received a weighed amount of carrots only. A limited number were observed in metabolism cages, from which the total amount of



Fig. 10.—Guinea-pig 35: A single injection of 5 mg. The animal was killed on the 117th day. Cystic dilatation of the glomerular capsule and moderate fibrosis with atrophy of the tubules, and some thickening of some of the glomerular capsules.

urine was collected and daily tests made. Bacterial growth in the urine was controlled by placing a few drops of chloroform in the receiving vessels. The ordinary clinical tests of the urine were applied, and quantitative estimations of the chlorid and phosphate excretion were made, using Volhard's method for the chlorids, and the

17. Siegel: Ein Stoffwechselversuch bei Urannephritis am Hunde. *Ztschr. f. exper. Path. u. Therap.*, 1907, iv, 561.

uranium nitrate method for the phosphates. The reaction was so alkaline that casts were rarely found in the twenty-four hour specimen. Autopsy was done in every case as soon after death as possible, and, in all cases where the animal was killed, chloroform was used, and the autopsy was done at once. Gross examination was made of all the organs, and histologic examination of the kidneys. Of the various fixing fluids tried, Carnoy's kidney fixative was found to give the best results, although sections fixed with this fluid could not be studied with Sudan III for the presence of fat. The blocks were embedded in paraffin, the sections cut at from four to six microns and mounted with glycerin and egg-albumen. The stains used were hematoxylin and eosin, Weigert's elastic tissue stain, Weigert's fibrin-stain (to demonstrate the hyaline change), and Van Gieson's connective tissue stain. The presence of calcium salts was demonstrated by von Kossa's silver nitrate solution.

Three series of experiments were made:

1. Eight animals (of which six are reported) were given very frequent subcutaneous injections of 0.25 mg. of uranium nitrate in aqueous solution, from 46 to 87 doses being given in from 77 to 120 days respectively. In this way it was hoped that I might simulate in a certain degree the long-continued mild intoxication which is considered to be an etiological factor in the development of the primary contracted or small red kidney.

2. Seven animals (of which five are reported) were given subcutaneous injections of 2.5 mg. of uranium nitrate at intervals of from 10 to 30 days, the number of doses and the interval being determined in each case by the reaction of the animal as indicated by the changes in the weight and the urinary picture. The dose was sufficient in each case to produce a definite nephritis, which however was not severe enough to kill the animal. In this way I hoped to be able to show the effect on the kidneys of repeated subacute attacks of nephritis.

3. Fourteen animals were given a single subcutaneous injection of 5 mg. of uranium nitrate, which was sufficient to produce a severe nephritis with extreme loss of weight and almost complete anuria. In two cases death followed within five days, in two cases on the seventh day, and in one case on the eighth day. Of the remaining nine animals two were killed on the twenty-fifth day, two on the one hundred and seventeenth day, one died on the two hundred and twenty-fourth day, two were killed on the two hundred and fortieth day; and

two animals were lost. This group (of which eight are reported) will show the condition of the kidneys at different periods after a single attack of acute nephritis.

#### PROTOCOLS.—SERIES I

PROTOCOL 1—*Guinea-pig 22*.—Eighty-two subcutaneous injections of 0.25 mg. of uranium nitrate were given during one hundred and ten days, after which the animal was killed. The weight decreased from 609 gm. to 455 gm. Albumin was present in the urine for four days following the fortieth dose, but was not observed again.

*Autopsy*.—The animal was fairly fat and showed no congestion of the peritoneum and no ascites. The kidneys appeared normal in size and color, and on section showed no macroscopic changes. The capsule stripped easily.

#### MICROSCOPIC EXAMINATION

The majority of the glomeruli show practically no change except that the tufts are dilated and completely fill the capsules. Many of the capsules, however, show definite thickening of the endothelium and of the basement membrane, while others are dilated, forming scattered microscopic cysts in the cortex. A few capsules contain a granular exudate but no desquamated cells. The tufts in nearly all cases show no changes except the dilatation described above, although a few have some thickening of the intervaseular connective tissue, and some others show slight fragmentation of the nuclei. The thickened basement membranes of the capsules show definite hyaline degeneration, but there is no hyaline change in the tufts.

The greater number of the convoluted tubules present a fairly normal appearance, although the epithelial cells are somewhat swollen. There are areas, however, where the tubules are distinctly dilated. In these areas the epithelium is flattened and degenerated, in some cases showing merely a narrow band of protoplasm with poorly staining nuclei inside the basement membrane. These tubules are found in the neighborhood of the glomeruli which show changes, and they contain a granular exudate and in many cases some desquamated epithelial cells. In other places the tubules are shrunk and atrophied and show a deposit of pigment. In the medullary rays the ascending limbs of Henle's loops are dilated and contain granular exudate and desquamated cells which show varying degrees of degeneration. The collecting tubules in the pyramids also contain exudate and debris, but otherwise show no change. A few of the tubules contain dense hyaline casts.

There are definite areas of round-cell infiltration in the interstitial tissue, in many cases widely separating the atrophied tubules which in these places show hyaline degeneration of their basement membranes. In a few cases these areas of round-cell infiltration are found around slightly damaged glomeruli. No changes can be observed in the walls of the blood vessels, and there are no areas of calcification.

PROTOCOL 2—*Guinea-pig 24*.—Fifty-one subcutaneous injections of 0.25 mg. of uranium nitrate were given during sixty-eight days, and the animal died on the sixty-eighth day. The weight decreased from 580 gm. to 415 gm. Albumin was present in the urine after the fourth, fourteenth and twenty-sixth doses for one day each time, after the thirty-second dose for three days, and after the forty-third dose for two days. There was almost complete anuria for the twenty-four hours preceding death, the small amount of urine excreted containing a high percentage of albumin. No convulsions were observed.

*Autopsy.*—The peritoneum was considerably congested and there was a small amount of clear fluid in the peritoneal cavity. The bladder contained about 5 c.c. of urine, which gave a definite reaction for albumin but contained no casts. The kidneys were rather large and pale, almost gray in color, with some dilated venules over the surface. There was no perinephric fat, and the capsule stripped easily. The cut surface bulged on section and showed some edema. The cortex was paler in color than the medulla.

#### MICROSCOPIC EXAMINATION

The condition found is similar to but more marked than that described in Protocol 1. There are a few definite areas of fibrosis which seem to replace the medullary rays, and which extend to and correspond with small dimples on the surface. Immediately on either side of these processes the greater part of the parenchymatous change is seen, the appearance of the cortex in other places being practically normal. The glomeruli show changes similar to those described in Protocol 1, but in addition, a few show newly formed elastic tissue fibers around the capsule, external to the thickened, hyaline basement membrane. The cystic formation is more marked and occurs both in the glomeruli and in the convoluted tubules, one cyst being found in the cortex which measured fully 1 mm. in diameter. The ascending limbs of Henle's loops contain greater numbers of desquamated cells but no dense hyaline casts. There are a few small foci of calcium deposit in the cortex and very definite deposit in the medulla.

*PROTOCOL 3—Guinea-pig 25.* (Figs. 1 and 2.)—Forty-six injections of 0.25 mg. were given in seventy-seven days, and the animal died on the seventy-seventh day. The weight dropped from 665 gm. to 410 gm. Albumin was present in the urine for two days after the fifth dose, and for two days before death. There was no noticeable tendency to anuria during the twenty-four hours preceding death, but numerous granular casts were found in the urine at this time.

*Autopsy.*—The peritoneum was markedly congested and firmly adherent to the abdominal wall in the region where the injections had been made. A very small quantity of fluid was found in the peritoneal cavity. The bladder was full of clear urine which gave a marked reaction for albumin and contained very many granular casts. The stomach and intestines were enormously distended and contained a large quantity of fluid material. The liver, heart, lungs and adrenals showed no gross change. The kidneys were very large, the left being larger than the right, and were dark in color and mottled. The capsule stripped easily. On section there was definite bulging and some edema, and the cortex and medulla were uniformly congested.

#### MICROSCOPIC EXAMINATION

The greater part of the cortex appears fairly normal, although the glomerular tufts completely fill the capsules, and the cells of the convoluted tubules are swollen and somewhat granular. Some of the glomeruli show thickened capsules with beginning proliferation of the endothelium, and some are surrounded by areas of round-cell infiltration. (Fig. 2.) The greatest change is seen in the medullary rays where the tubules are dilated, their epithelium flattened, and their lumens filled with exudate and desquamated cells. (Fig. 1.) Many of the convoluted tubules in the vicinity show a similar change, and there are areas at and near the cortical margin where the same condition obtains. There are some desquamated cells and exudate in the lumens of the collecting tubules. There are no areas of definite fibrosis, but there are

many areas of round-cell infiltration occurring chiefly near the junction of the cortex and medulla, and frequently in close relation to the medium-sized veins. There are no dense hyaline casts in the tubules and very little hyaline degeneration of the basement membranes. A few small patches of calcification are seen in the medulla.

PROTOCOL 4—*Guinea-pig 26.* (Fig. 3.)—Thirty-six injections of 0.25 mg. were given in forty-five days, and the animal died on the forty-fifth day. The weight dropped from 587 gm. to 480 gm. Albumin was present in the urine for one day after the eighth dose and for one day before death. There was almost complete anuria for sixteen hours before death, but no convulsions were observed.

*Autopsy.*—The peritoneum was definitely congested, and was adherent to the abdominal wall in the region where the injections had been made. There was a considerable amount of clear fluid in the peritoneal cavity. The bladder contained about 7 c.c. of clear urine, which gave a definite reaction for albumin and contained granular casts, some epithelial cells, and a few leucocytes. The stomach and intestines were distended and were filled with a fluid material. The heart, lungs, liver and adrenals showed no gross changes. The kidneys were about normal in size and color. The capsule stripped easily and there was some bulging of the cut surface on section.

#### MICROSCOPIC EXAMINATION

The condition shown is very little different from that described above. There is no definite fibrosis, but there are many areas of round-cell infiltration, and a fair number of glomeruli with thickened capsules which are surrounded with atrophied tubules. There is definite hyaline degeneration of the basement membranes, both of the tubules and of the glomerular capsules, and there is some cyst formation, chiefly of the glomeruli. The epithelium of the tubules is not granular, but many of the tubules are dilated, have flattened epithelium, and contain exudate and desquamated cells in their lumens. (Fig. 3.) Many dense hyaline casts are present in the tubules, but no areas of calcification are seen.

PROTOCOL 5—*Guinea-pig 30.*—Eighty-three injections of 0.25 mg. were given in one hundred and twenty days, and the animal was killed on the one hundred and fifty-seventh day. The weight fell from 540 gm. to 470 gm. during the time the injections were being made, but went up to 615 gm. during the following thirty-seven days. The urine was not observed until after the forty-sixth dose. Albumin was present in the urine for three days after the fifty-first dose, and for four days after the fifty-seventh dose. No casts were found.

*Autopsy.*—The peritoneum was not congested, there was a very small amount of clear fluid in the peritoneal cavity, and all the organs, including the kidneys, appeared normal on gross examination.

#### MICROSCOPIC EXAMINATION

There is much less change than in the preceding animals, but there are a number of glomerular cysts which are surrounded by degenerated and atrophied tubules. Some of the glomerular capsules contain exudate, and a few of them have thickened basement membranes which have undergone hyaline degeneration. There is less tubular change than in the preceding cases, but some of the tubules are dilated and have exudate and debris in their lumens. No dense hyaline casts are seen. There are a number of areas of round-cell infiltration scattered through the cortex, but there is no definite fibrosis. There is no new formed elastic tissue, and no deposit of calcium salts.

PROTOCOL 6—*Guinea-pig 36*.—Eighty-seven injections of 0.25 mg. were given during one hundred and eight days, and the animal was killed on the one hundred and eighth day. The weight dropped from 572 gm. to 510 gm. No albumin was observed in the urine.

*Autopsy*.—There was no congestion of the peritoneum, but a small amount of fluid was found in the peritoneal cavity. The liver, lungs, heart and adrenals showed no gross changes. The kidneys were rather large but normal in color. Immediately beneath the capsule at the lower pole the left kidney contained a large cyst, about the size of a No. 6 shot, which was filled with a clear fluid. No other cysts were seen, and on section the kidney substance appeared quite normal.

#### MICROSCOPIC EXAMINATION

There is much more change in the kidney substance than one would have expected to find from looking at the gross specimen. There are many areas of round-cell infiltration and many areas of beginning fibrosis which extend to and correspond with definite though microscopic dimples on the surface of the kidney. There are rather numerous microscopic cysts which are derived from both glomeruli and tubules, and which contain a homogeneous exudate. Some of these cysts are surrounded by dense round-cell infiltration, and others, which are larger, have compressed the tubules which lie near them. Many of the cysts show merely a flattened band of epithelium which is degenerated and possesses very poor staining properties, and many of them have a definitely thickened basement membrane. Some of the glomeruli show thickening and hyaline degeneration of the basement membrane, while others contain exudate and desquamated cells. Many of the tubules are dilated and contain exudate and debris, and many of them are atrophied and show hyaline change in their basement membranes. No dense hyaline casts or newly formed elastic fibers are seen. There is no deposit of calcium salts.

#### PROTOCOLS.—SERIES II

PROTOCOL 1—*Guinea-pig 21*. (Figs. 4, 5 and 6.)—Six subcutaneous injections of 2.5 mg. were given during a period of seventy-seven days. The doses were given on the first, second, twenty-seventh, forty-seventh, sixtieth and seventieth days, and the animal died on the seventy-seventh day. No examination of the urine was made immediately after the first two doses. There was definite albumin excretion for four days after the third dose, and two days later there was a faint trace for one day. Albumin was not observed again until after the sixth dose when it was present for the six days preceding death. There was rather marked irregularity of the chlorid and phosphate excretion in the urine throughout the experiment, with definite retention after the third and fifth doses, in the latter case occurring without any albuminuria. Following the sixth dose there was marked irregularity of the chlorids without definite retention, but there was a very definite phosphate retention. There was definite loss of weight after the second, third and sixth doses, and the animal dropped from 732 gm. to 455 gm. during the experiment. Figure 4 shows the effects of the third, fifth and sixth doses.

*Autopsy*.—The animal was rather thin. There was some congestion of the peritoneum but no fluid in the peritoneal cavity. The bladder contained about 5 c.c. of urine which showed a trace of albumin, some leucocytes and many granular casts. The kidneys were about normal in size with little fatty capsule. They were pale in color, slightly mottled, and showed numerous uneven depressions on the surface. On section there was no bulging and no edema, and the cortex was paler and narrower than normal. There was a

considerable amount of fluid in the pericardial sac. The other organs appeared normal in the gross except for a large bunch of cysts which were attached to the cystic duct.

#### MICROSCOPIC EXAMINATION.

There is a very definite sclerotic change involving the greater part of the cortex, although it is most marked near the junction of the cortex and medulla. From this deeper part numerous processes pass out towards the margin, and in some places correspond to definite dimples on the kidney surface, though in the majority of cases there is a narrow layer of more or less normal cortex between these processes and the margin. There are a few small cysts scattered throughout the cortex, the majority of which are glomerular in origin. There are very marked degenerative changes in the glomeruli. In most cases there is very little damage to the tufts, but in a few cases there are varying degrees of proliferation of the connective tissue, and in a few there is complete destruction with hyaline degeneration. The capsules are very much thickened with swollen hyaline basement membranes, and with some proliferation of the endothelium. There are no desquamated cells or exudate in the intracapsular spaces. (Fig. 5.) Surrounding many of the capsules just external to the basement membrane, there is a definite new formation of elastic tissue, which in some cases seems to be continuous with that of the small arteries of the cortex. (Fig. 6.) In most cases there is very extensive connective tissue proliferation around the changed glomeruli, but in some cases the glomeruli seem to be isolated spots of fibrosis which are surrounded by quite normal appearing parenchyma.

The majority of the tubules are involved in the fibrotic changes described above, although at the margin of the cortex, and between the processes of fibrosis which extend to the surface, there are areas of tubules which show practically no change. The damaged tubules are in the main atrophied and compressed, in many cases being represented by bunches of poorly stained nuclei, but some are dilated, having flattened epithelium, and others are distinctly cystic. The dilated tubules contain a granular exudate and desquamated epithelial cells. The basement membranes in many cases are thickened and show hyaline degeneration, but there is no elastic tissue proliferation around the tubules.

The newly formed connective tissue is rich in nuclei throughout, and there are also areas of dense round-cell infiltration. There is a finely granular deposit of calcium salts scattered rather uniformly throughout the fibrotic areas in the cortex. The tubules in the medulla and in the medullary rays are somewhat dilated and contain desquamated cells, exudate, and some dense hyaline casts in their lumens. There is practically no proliferation of connective tissue in the medulla, but there are a few scattered areas of calcium deposit.

PROTOCOL 2—*Guinea-pig 23*. (Fig. 7.)—Six subcutaneous injections of 2.5 mg. were given during a period of seventy days. The doses were given on the first, second, thirty-fifth, fifty-seventh, sixty-third and seventieth days, and the animal died on the seventy-third day. Albumin was present in the urine for four days after the fifth dose, and for the three days after the sixth dose which preceded death. Granular casts were found after the sixth dose. There was a definite increase in the amount of urine excreted during the last two weeks of the experiment, the output for the last eighteen days averaging 123 c.c. per day as compared with 94 c.c. per day for the thirty-one days preceding. The excretion of the salts increased somewhat with the increase in the amount of urine, but the specific gravity for the last eighteen days averaged only 1019 as compared with 1022 for the preceding thirty-one days. There was a definite diminution in chlorids and phosphates after the third, fifth and



sixth doses. The animal lost weight after the second, third, fourth and sixth doses, dropping from 680 gm. to 412 gm. during the experiment. The reaction was less marked after every injection than in Guinea-pig 21. Figure 7 shows the reaction after the third, fifth and sixth doses.

*Autopsy.*—The animal was emaciated, the peritoneum was somewhat congested, and there was a small amount of fluid in the peritoneal cavity. There was a small amount of urine in the bladder which showed some albumin and many granular casts. The kidneys were slightly swollen and mottled, and had no fatty capsule. On section there was some bulging of the cut surface and a slight uniform congestion of both cortex and medulla. The other organs appeared normal on gross examination.

#### MICROSCOPIC EXAMINATION.

There is remarkably little change as compared with that found in Guinea-pig 21. The greater part of the cortex appears normal although a number of the glomeruli have thickened capsules with some proliferation of the endothelium. There is no exudate and no desquamation of endothelium into the capsular space. There is some increase in the connective tissue of the tufts and some hyaline change in the basement membranes of the capsules, but there is no new formation of elastic tissue. Some of the tubules are dilated, having flattened epithelium and containing exudate and debris in their lumens. There are a few casts in the loops of Henle, and a few areas of round-cell infiltration which are chiefly in the region of the larger veins. There are no definite areas of fibrosis, and there is no deposit of calcium salts.

**PROTOCOL 3**—Guinea-pig 28.—Seven subcutaneous injections of 2.5 mg. were given during a period of ninety-four days. The animal survived and was killed on the one hundred and forty-first day. The injections were given on the third, eighteenth, thirty-third, forty-sixth, sixty-ninth, eighty-sixth and ninety-fifth days. The urine was observed for a short time only in the early part of the experiment. Albuminuria was present after the fifth and seventh doses, and the chlorid and phosphate excretion was very irregular at this time. The animal lost weight after all except the third injection. The weight dropped from 580 gm. to 420 gm. during the period of injection, but increased to 610 gm. during the following forty-two days.

*Autopsy.*—The animal was very fat, the peritoneum was not congested, and there was no fluid in the peritoneal cavity. There was a large amount of perinephric fat, and the kidneys were rather small and mottled. In places the surface was distinctly dimpled, and in these areas the capsule was adherent. On section the cortex appeared paler than the medulla, and was narrower than normal. The small amount of urine in the bladder contained neither albumin nor casts. The other organs appeared normal on gross examination.

#### MICROSCOPIC EXAMINATION.

There are many patches of fibrosis scattered through the cortex, and some of these extend to the surface and correspond to the dimples on it. The fibrotic areas are not confined to the inner zone of the cortex, but are irregularly scattered through it. There are a good many small cysts, most of which are glomerular in origin. The majority of the glomeruli have thickened capsules, some have proliferation of the endothelium, and other show some fibrosis of the tufts. There is no exudate into the intracapsular spaces. There is hyaline degeneration of the thickened basement membranes of the capsules, and in some cases there is a new formation of elastic tissue. In the areas of fibrosis there are bunches of glomeruli which show the changes described, and

scattered through the more normal appearing cortex there are many single glomeruli which show a similar condition. The convoluted tubules do not show much atrophy except in the sclerotic areas, but around the changed glomeruli there are some dilated tubules with flattened epithelium which have exudate and desquamated cells in their lumens. The collecting tubules and the loops of Henle also contain exudate and a few cells. There is some hyaline degeneration of the basement membranes of the tubules in the fibrotic areas, but there is no new formation of elastic tissue. There is some deposit of calcium salts in the medulla, but none in the cortex.

**PROTOCOL 4—Guinea-pig 34.**—Six subcutaneous injections of 2.5 gm. were given during a period of eighty-three days. The doses were given on the second, twenty-second, thirty-sixth, forty-sixth, sixty-fifth and eighty-third days, and the animal died on the ninety-seventh day. The urine was observed for a short time only. Albumin was found after the fifth and sixth doses, and the excretion of salts was very irregular. The animal lost weight after the second, third, fourth, fifth and sixth doses, and continued to lose weight during the fourteen days which preceded death. The total loss of weight was from 547 gm. to 250 gm. The reaction after each injection was very severe, the animal becoming acutely ill each time.

**Autopsy.**—The animal was very thin and the peritoneum was somewhat congested, but there was no fluid in the peritoneal cavity. A very small amount of urine in the bladder gave a definite test for albumin, but unfortunately an examination for casts was not made. The kidneys were very small and distinctly granular, but had no fatty capsule. The capsule was rather firmly adherent to the surface of the kidney. On section the kidney substance was firm, the cortex thin and pale, and the medulla dark. The other organs appeared normal on gross examination.

#### MICROSCOPIC EXAMINATION

There is very definite proliferation of the connective tissue throughout the cortex with marked destruction of the glomeruli and tubules. The glomeruli show marked thickening of the capsules with hyaline degeneration of the basement membranes and new formation of elastic tissue. There is definite increase in the connective tissue of the tufts, which appear much more dense than in any of the other cases. Many of the tubules are atrophied and shrunk; others are dilated, having flattened epithelium, and contain exudate in their lumens. There is very little desquamation of the epithelial cells. There are very dense hyaline casts in the loops of Henle and in the smaller collecting tubules. The connective tissue proliferation is very widely distributed and extends well down into the medulla where it separates the tubules in a rather marked degree. The connective tissue is sparsely nucleated and there are no areas of round-cell infiltration. There is very marked calcium deposit in both medulla and cortex, the calcification being so marked as quickly to destroy the edge of the knife when cutting sections.

**PROTOCOL 5—Guinea-pig 37.**—Six subcutaneous injections of 2.5 mg. were given during a period of one hundred and eleven days, and the animal was killed on the one hundred and thirty-fourth day. Albumin was present in the urine after the first, fifth and sixth doses, the only times at which observations were made. There was definite retention of salts after the first dose, and a very irregular excretion after the fifth and sixth doses. There was a definite increase in the amount of urine excreted during the latter part of the experiment. During the first nine days the average output was 89 c.c. per day with an average specific gravity of 1020, and during the last fifteen days the

average excretion was 100 c.c. per day with an average specific gravity of 1018. The animal lost weight after the first, third and sixth doses, dropping from 495 gm. to 405 gm. during the experiment.

*Autopsy.*—A small amount of fluid was found in the peritoneal cavity, but the bladder was practically empty. The kidneys were small, somewhat pale in color, and were slightly granular on the surface. On section there was no bulging and no edema, the consistency was somewhat more resistant than normal, and the cortex was rather narrow.

#### MICROSCOPIC EXAMINATION

There is a very marked fibrosis of the cortex of the kidney with extensive destruction of the tubules and glomeruli. The new formed connective tissue is very rich in cells, and is quite diffuse. It is most marked in the inner zone of the cortex, but there are many processes which extend to the surface of the kidney, and which correspond to the dimples on the surface. The majority of the glomeruli show thickening of their capsules, proliferation of their endothelium, and hyaline degeneration of their basement membranes. Many of the tufts are condensed and fibrous, and a few show more or less hyaline change. There are many small glomerular cysts, some of which contain exudate, and there is new-formed elastic tissue around some of the glomeruli. In some areas the tubules appear fairly normal, but in many places they are dilated, have flattened epithelium, and contain exudate in their lumens, and in other places they are more or less completely atrophied, in some places being represented by bunches of poorly staining nuclei. The loops of Henle and the collecting tubules contain exudate and debris, and many of the loops contain dense, fragmented, hyaline casts. There is some hyaline degeneration of the basement membranes of the shrunken tubules, but there is no newly formed elastic tissue around them. There are many areas of calcification in the cortex, and some in the medulla.

#### PROTOCOLS.—SERIES III

PROTOCOL 1—*Guinea-pig 32.*—A single injection of 5 mg. was given subcutaneously, and the animal died four days later. The loss in weight was about 25 gm.

*Autopsy.*—The peritoneum was slightly congested, but there was no fluid in the peritoneal cavity. The kidneys were dark in color, and larger and less firm than normal. The capsule stripped easily. On section there was definite bulging of the cut surface and some edema, and both cortex and medulla were distinctly congested.

#### MICROSCOPIC EXAMINATION

There is very marked congestion of the kidneys and an extreme degree of damage to the convoluted tubules, but there is very little change in the glomeruli. The only indication of interstitial change is seen in a few areas of round-cell infiltration around some of the small veins. The glomeruli are practically normal in appearance, although there is slight congestion of the tufts, and in a few cases some exudate into the intracapsular space. There is no thickening of the capsule, and no desquamation or thickening of the capsular endothelium. The convoluted tubules are practically all enormously degenerated; many of them are dilated with their epithelium flattened and their lumens filled with exudate, and many are practically denuded of their epithelium. Those tubules where the damage is less severe show cloudy degeneration of the cells and almost complete obliteration of their lumens. The ascending

limbs of Henle's loops are greatly dilated and contain exudate and desquamated cells, and the smaller collecting tubules also contain considerable debris. A few hyaline casts are seen in the tubules. There is no deposit of calcium salts.

PROTOCOL 2—*Guinea-pig 148*.—A single injection of 5 mg. was given subcutaneously, and the animal died five days later. There was a very heavy excretion of albumin in the urine for the four days preceding death, and there was also some copper-reducing substance which gave a very marked "sugar" reaction, for three days preceding death. The animal dropped in weight from 570 gm. to 295 gm.

*Autopsy*.—The peritoneum was congested, but there was no fluid in the peritoneal cavity. The kidneys in the gross and microscopically were practically the same as those described in Protocol 1 of this series.

PROTOCOL 3—*Guinea-pig 16*.—A single injection of 5 mg. was given subcutaneously, and the animal died on the eighth day. The weight dropped from 530 gm. to 380 gm. No analysis of the urine was made.

*Autopsy*.—There was marked congestion of the peritoneum, but no fluid in the peritoneal cavity. The kidneys were swollen, and on section showed some edema and some bulging of the cut surface. The capsule stripped easily. The other organs showed no gross changes.

#### MICROSCOPIC EXAMINATION

There is very definite congestion of the arterioles and of the glomeruli. There are numerous rather large cysts scattered throughout the cortex, many of which are tubular in origin though some are glomerular. Many of the glomeruli are unchanged except for the congestion of the tufts, but some have exudate into the glomerular capsule, a few show some proliferation of the capsular endothelium, and an occasional one shows some thickening of the basement membrane of the capsule. The majority of the tubules show very little change except for some cloudy swelling of the epithelium. Some of the tubules are dilated, having flattened epithelium, and containing exudate and debris in their lumens, and some of them show calcium deposit in the cells of the tubules and in the desquamated cells in their lumens. The loops of Henle and the smaller collecting tubules have some exudate in their lumens, and a few contain hyaline casts. There are a few areas of round-cell infiltration and a good deal of calcium deposit in the cortex. There is no new formation of elastic tissue.

PROTOCOL 4—*Guinea-pig 19*. (Fig. 8).—A single injection of 5 mg. was given subcutaneously, and the animal was killed on the twenty-fifth day. The weight dropped from 545 gm. to 360 gm. during the first fifteen days, but increased to 405 gm. during the following ten days. No analysis of the urine was made.

*Autopsy*.—There was no congestion of the peritoneum, but there was a small amount of fluid in both the pleural and peritoneal cavities. Neither kidney had any fatty capsule. The right kidney was slightly swollen and very pale though mottled in color. On section there was some bulging of the cut surface which had a peculiar grayish color. There was a fine striation of calcareous infarction along the outer margin of the medulla. The left kidney was much smaller than the right, and was chalky white in color. On section the whole cut surface of the kidney was uniformly white and the pelvis of the kidney was filled with a milky white fluid which contained a few leucocytes, and numerous small white globules which dissolved with effervescence in dilute acid. The other organs showed no gross changes.

## MICROSCOPIC EXAMINATION

The type of change found is very similar in both kidneys, but has progressed much farther in the left than in the right. The right kidney shows an outer zone of cortex (about one-half the width of the cortex), in which there is very little change in either the glomeruli or the tubules. The inner half of the cortex, however, shows very definite change. The capsules of the glomeruli are very much dilated, forming small cysts. There is no thickening of the basement membrane of the glomeruli, and except in a few cases there is no proliferation of the endothelium. The tufts are slightly shrunken but not collapsed, and they show no increase in their connective tissue elements. The intracapsular space is dilated to about five-thirds its original size, and in most cases does not contain any exudate. (Fig. 8.)

The tubules of the inner zone show varying degrees of change. Some are dilated, having flattened epithelium and containing exudate in their lumens, while others are collapsed and show a moderate though not an advanced degree of atrophy of the epithelium. In these areas the tubules are separated by a recent cellular proliferation of the interstitial tissue. There are very many fragmented hyaline casts in the ascending limbs of Henle's loops, and there is exudate and desquamated cells in some of the collecting tubules. There are a few small patches of degenerated tubules in the outer zone of the cortex which show some increase in their cellular elements, and which correspond to microscopic dimples on the surface of the kidney. There are many large areas of round-cell infiltration in the inner zone of the cortex which are mostly situated in the neighborhood of the larger veins. There is no hyaline change in the basement membranes of the glomerular capsules or of the tubules, and there is no new formation of elastic tissue.

The left kidney, which was the smaller, presents a much more advanced degree of change. The condition described in the inner zone of cortex in the right kidney, is found throughout the whole cortex of the left kidney, so that there is practically no normal appearing parenchyma left. Almost all the glomerular capsules are dilated and show no thickening of their basement membranes, although a very few have a slight proliferation of the endothelial cells. Practically all the tubules are degenerated, some being dilated and containing exudate and desquamated cells, while others are collapsed and more or less completely atrophied. Many of the loops of Henle contain casts, some of which are hard and fragmented, and many of the collecting tubules contain exudate and desquamated cells. There is definite increase in the intertubular connective tissue, and there are many areas of round-cell infiltration. There is no hyaline degeneration of the basement membranes of either the tubules or the glomeruli, and there is no new formation of elastic tissue. There are several areas where calcium granules are seen inside the cells of the degenerating epithelium.

PROTOCOL 5—*Guinea-pig 33*. (Fig. 9.)—A single injection of 5 mg. was given subcutaneously, and the animal was killed in one hundred and seventeen days. No analysis of the urine was made. The weight dropped from 520 gm. to 387 gm. during the first ten days, but subsequently increased to 505 gm.

*Autopsy*.—The peritoneum was not congested, but there was a small amount of fluid in the peritoneal cavity. Both kidneys were small, the left being smaller than the right, and both were red in color, distinctly granular, and surrounded by a well marked fatty capsule. The true capsule was adherent in both kidneys, and on section the cortex appeared narrower than normal. There was no bulging of the cut surface and no edema.

## MICROSCOPIC EXAMINATION

The picture presented is that of an advanced interstitial nephritis. There is very great destruction of the renal tissue, marked proliferation of the connective tissue, extensive cyst formation, and definite irregularity of the surface of the kidney. (Fig. 9.) The most marked degree of change is in the inner zone of the cortex, but large areas of fibrosis extend to the surface and correspond to the depressions on it. The glomeruli show very marked change throughout. In the inner zone of the cortex many of them are cystic, varying in size of from two to three times their normal diameters. Some of them are empty, some show remnants of their more or less compressed tufts, and others contain exudate and desquamated cells. Their capsules show considerable thickening, notwithstanding the fact that they are so greatly distended. The glomeruli in the peripheral zone are about normal in size, but there are practically none which do not show more or less definite change. The tufts completely fill the intracapsular spaces, and show some fibrosis and some fragmentation of the nuclei, but no hyaline change. The capsules are very much thickened, there is definite hyaline degeneration of the basement membranes, and in many cases marked proliferation of the endothelial layer. Many of the glomeruli and cysts are surrounded by newly formed elastic tissue which is situated immediately outside the thickened basement membrane.

The convoluted tubules are also very much damaged. There are a few small areas where the tubules have a fairly normal appearance, but even here there is an increased number of intertubular nuclei, and in many cases the tubule is completely isolated by a thin but definite layer of connective tissue which surrounds it. The vast majority of the tubules are atrophied and shrunk, being represented by a ring of small misshapen nuclei. In some cases there is a small lumen which contains a granular exudate and desquamated cells, but there is no dilatation of the convoluted tubules. Many of the degenerated cells contain a fine granulation of calcium deposit, and the basement membranes of the atrophied tubules show marked hyaline degeneration. Many of the ascending limbs of Henle's loops are dilated to several times their normal diameter, and are lined by very much flattened and degenerated epithelium. Many of these tubules are empty, but some of them contain exudate and desquamated cells, and others contain dense, fragmented, hyaline casts. Many of the collecting tubules contain exudate and debris.

There is very marked proliferation of a richly cellular connective tissue especially in the cortex where it extends to the surface and corresponds to the depressions which are found on it. There are very definite areas of round-cell infiltration, some of which are associated with the larger veins. There are some areas of calcium deposit in the medulla.

PROTOCOL 6—*Guinea-pig 35*. (Fig. 10.)—A single injection of 5 mg. was given subcutaneously, and the animal was killed on the one-hundred-and-seventeenth day. The weight dropped from 540 gm. to 460 gm. during the first eight days, but had increased to 530 gm. at the time of death. No analysis of the urine was made.

*Autopsy*.—The animal was fat and there was no congestion of the peritoneum. There was a small amount of fluid in the peritoneal cavity. The kidneys were somewhat swollen and rather pale. The left kidney had a large cyst, about the size of a BB shot, situated in the upper pole at the inner margin of the cortex. The other organs showed no changes visible on gross examination.

## MICROSCOPIC EXAMINATION

The type of change closely resembles that described in Protocol 5, although it is much less marked in degree. There is rather extensive fibrotic change in the inner zone of the cortex, but only in a few places does the fibrosis extend to the surface of the kidney and cause a depression on it. There are much larger areas of normal appearing cortex, but here too, there are many tubules which are completely surrounded by thin processes of connective tissue. Many of the glomeruli in these areas show little if any change, but some have thickened capsules with proliferation of the endothelial layer. In the inner zone, however, the condition closely resembles that found in Guinea-pig 33. There is definite cyst formation, extreme atrophy of the tubules, marked proliferation of the connective tissue, and thickening of the glomerular capsules. (Fig. 10.) There is no marked dilatation of the loops of Henle, but many of them are filled with exudate and desquamated cells, and others contain dense fragmented casts. Many of the collecting tubules contain exudate and debris. There is marked hyaline degeneration of the basement membranes of the thickened capsules and atrophied tubules, and there is definite new formation of elastic tissue around some of the glomeruli. There is some granular calcium deposit in the degenerating epithelium, and some scattered areas of calcification in the medulla.

PROTOCOL 7—*Guinea-pig 47*.—A single injection of 5 mg. was given subcutaneously, and the animal was killed on the two-hundred-and-fortieth day. The weight dropped from 580 gm. to 335 gm. in the first ten days, but had increased to 475 gm. on the seventeenth day. It was not observed at time of death. There was a steady decrease in the amount of urine during the first twelve days until there was almost complete anuria. Albumin appeared in the urine on the third day after the injection and was still present on the seventeenth day. The "sugar" reaction appeared on the third day and lasted four days. No further examinations of the urine were made during the life of the animal, but after death there was a small amount of urine in the bladder which contained a few leucocytes, some epithelium and a few granular casts.

*Autopsy*.—The animal was very fat, the peritoneum was slightly congested, and there was a small amount of fluid in the peritoneal cavity. The kidneys were not swollen but were somewhat pale and rather mottled. The capsule stripped easily. On section there was no bulging of the cut surface and no edema. The other organs appeared normal on gross examination.

## MICROSCOPIC EXAMINATION

The cortex of the kidney shows many small cysts which are mostly glomerular in origin. Many of the glomeruli have thickened capsules with hyaline degeneration of their basement membranes, and a few are surrounded by newly formed elastic tissue. Many of the convoluted tubules are dilated, having flattened epithelium and containing exudate and desquamated cells in their lumens, and many of the loops of Henle are blocked with dense, fragmented, hyaline casts. There is no marked diffuse new growth of the intertubular connective tissue, and there are no areas of round-cell infiltration. There are a few areas of calcium deposit occurring chiefly in the medulla.

PROTOCOL 8—*Guinea-pig 44*.—A single injection of 5 mg. was given subcutaneously, and the animal died on the two-hundred-and-twenty-fourth day. The weight dropped from 510 gm. to 440 gm. during the first six days, and the animal weighed 385 gm. at time of death. There was no decrease in the amount of urine excreted after the injection, but there was definite albuminuria commencing on the second day and persisting throughout the seven days during

which observations were made. The "sugar" reaction appeared on the second day and lasted for four days. The animal gained weight rapidly after the first ten days, and remained in apparently good health until within a few days before death.

*Autopsy.*—The peritoneum was slightly congested, and there was a small amount of fluid in the peritoneal cavity. The kidneys were somewhat swollen and mottled, and the capsule stripped easily. The cortex appeared normal. There was no urine in the bladder.

#### MICROSCOPIC EXAMINATION

The appearance is very much the same as that described in Protocol 7, although there is not quite so much glomerular change. There are many normal glomeruli, but there are also many glomerular cysts, and many glomeruli with thickened capsules, hyaline basement membranes, and new formed elastic tissue. Some of the convoluted tubules are dilated and have exudate and debris in their lumens. Many of the loops of Henle are blocked by dense, fragmented casts, and many of the collecting tubules contain exudate and desquamated cells. There are some small areas of fibrosis which are rich in nuclei, and which in some places correspond to dimples on the surface of the kidneys, but there is no diffuse proliferation of the intertubular connective tissue. There is some deposit of calcium salts in the medulla.

#### DISCUSSION

Before discussing the significance of the foregoing experiments it may be well to refer briefly to an objection which will undoubtedly be raised. It is well known that small animals are subject to spontaneous kidney lesions, and that conditions are occasionally found which more or less closely resemble that of chronic interstitial nephritis in man. In view of this fact one must be careful that a condition which may be coincident with, be not interpreted as resultant from the administration of some renal irritant.

In our series of experiments sixteen animals which died as a result of acute poisoning with uranium nitrate and four which were killed as normal controls were carefully examined for evidences of chronic lesions. Of these twenty animals not one showed any condition which at all resembled those described above (excepting, of course, the two acute cases described in Protocols 1 and 2 of Series III). In one animal which succumbed to acute poisoning a single glomerulus was found which showed slight thickening of the endothelium, but in no case was there any thickening of the capsule or hyaline degeneration of the basement membrane, and in none of the kidneys of the normal controls was there any appearance of round-cell infiltration.

On the other hand, in Series I, in which eight animals were subjected to experiment, one was killed after a few injections but before anything was found, one died from acute poisoning with sodium chlorid and so could not be included in the series, and the other six are



reported. And in Guinea-pig 31 which died from sodium chlorid poisoning, the kidneys showed glomerular and tubular lesions which were undoubtedly not due to the terminal insult.

In Series II, in which seven animals were injected, five are reported. One animal, No. 29, received seven injections but showed practically no reaction at any time, and, when killed after one hundred and thirty-four days, showed no definite or characteristic lesions. Another animal, No. 38, was killed by an overdose of sodium chlorid and so could not be included in the series. Animals 21, 28, and 34 which showed the most marked reaction during life showed also the most severe kidney lesions after death.

In Series III, in which fourteen animals were injected, two died within five days and are reported as examples of acute poisoning, two were lost, and six of the others are reported. In only one instance, Animal 20, was there a complete absence of kidney lesion; the other three all showed definite changes which in kind, though not in degree, resembled those described in the cases reported.

Now when it is considered that in the examination of twenty animals which had not been subjected to experiment not one was found which showed any chronic lesions; that out of twenty-seven animals subjected to treatment only two failed to show some definite and characteristic change; and that in all three series those animals which reacted most actively during life showed the most marked degrees of change after death; I think I am justified in assuming that the lesions which were found were due to the administration of Uranium Nitrate.

From 1885 to 1889 Chittenden with Hutchinson and Lambert<sup>18</sup> investigated the pharmacology of uranium nitrate, and noted that in dogs it produced acute parenchymatous nephritis which was associated with albuminuria and later with glycosuria. It was not until after Richter's report<sup>6</sup> in 1904, however, that especial attention was paid to the action of this drug as a renal irritant. Since that time it has been extensively used in the production of experimental nephritis, but the attention of investigators seems to have been almost exclusively focused upon a study of the process of edema formation which is associated with acute poisoning with this drug. Indeed if I exclude Siegel's<sup>17</sup> reference to an incipient chronic change in the kidneys of a single dog, I have been unable to find any reference in the literature to the use of uranium nitrate in attempts to produce chronic nephritis in animals.

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18. Chittenden and others: Cited from Tylecote: Pharmacology and therapeutics of uranium. *Med. Chron.*, Manchester, 1904, 379.

Schlayer and Hedinger<sup>19</sup> and Takayasu<sup>20</sup> have investigated the reaction of normal and damaged kidneys to stimuli of various kinds, and they found that kidneys damaged by uranium nitrate, together with those damaged by potassium bichromate and corrosive sublimate, constitute a group which they designate as "tubular," in contrast to those damaged by cantharidin and arsenic, which they designate as "vascular." Histologically they found that in the tubular group of nephritis the epithelium of the tubuli contorti suffered the greatest damage, while that of the straight and collecting tubules remained intact. They also found slight injury to the Malpighian corpuscles, but they state that this was more marked in those kidneys which were poisoned by potassium bichromate. Takayasu<sup>20</sup> says that the tubular change is the characteristic feature of the tubular group, and that the glomeruli show definite changes only comparatively late. He says that even in cases of severe functional disturbance there is very slight damage to the glomeruli. Desquamation of the capsular endothelium is seen in only a few cases, and in very slight degree. The blood content of the glomeruli is normal, and there is no change in the tufts. There is no increase in the number of the nuclei in the glomeruli although in some cases they show distinct enlargement and loss of staining power. He points out, however, that these latter changes are especially seen in the bichromate kidneys, and that they are present in a much less degree in the uranium and corrosive sublimate kidneys, not more than 20 per cent of the nuclei of the uranium kidneys being so changed.

Christian<sup>21</sup> has recently reported the occurrence of small round or oval, homogeneous, hyaline droplets, which he found in the glomerular tufts of thirteen out of twenty-six rabbits examined, and of these thirteen, eleven were animals which had been poisoned by uranium nitrate. The droplets appear in the wall of the capillaries which make up the glomerular tufts, and do not occur in the lumen of the capillaries, or in the space between the tuft and the capsule of the glomerulus, or in the endothelium of Bowman's capsule.

Protocols 1 and 2 in Series III describe the histologic picture which I found in the acute intoxications. The convoluted tubules

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19. Schlayer and Hedinger: Experimentelle Untersuchungen über toxische Nephritis. *Deutsch. Arch. f. klin. Med.*, 1907, xc, 1.

20. Takayasu: Ueber der Beziehungen zwischen anatomischen Glomerulusveränderungen und Nierenfunktion bei experimentellen Nephritiden. *Deutsch. Arch. f. klin. Med.*, 1907, xcii, 127.

21. Christian: A glomerular lesion of experimental nephritis. *Boston Med. and Surg. Jour.*, 1908, clix, 8.

and the ascending limbs of Henle's loops showed early and marked degeneration, and contained exudate and desquamated cells. The epithelium of the ascending limbs of Henle seemed to be the earliest cells affected, and there was marked degeneration and desquamation of these cells while those of the convoluted tubules were still relatively intact. The collecting tubules contained exudate and debris, but showed no degeneration of the epithelium. There was some congestion of the glomeruli, and slight exudate into the intracapsular space in a few cases, but we did not observe the nuclear changes described by Takayasu or the hyaline droplets described by Christian. There was some change in the interstitial tissue as was shown by the areas of round-cell infiltration in those cases which survived for a few days, but there was no thickening of the glomerular capsules, and no visible increase in the intertubular connective tissue. The feature to which I would draw especial attention in the acute poisoning is the extreme degree of change in the tubules, and the very insignificant amount of change in the glomerular tufts and capsules.

In Series I, in which repeated small doses were given, the results obtained, while perhaps not very marked, were sufficiently uniform and striking to justify further observations over a longer period of time. It is unnecessary to repeat in detail the picture described in the protocols, but I may briefly draw attention to the following facts. Five of the six animals reported showed albuminuria at some time during the course of the experiment, and of the three which died as a result of the injections, two showed very definite anuria before death. At autopsy five were found to have a certain amount of ascites, and of the four cases where urine was present in the bladder, in one the urine contained albumin but no casts, in two it contained albumin and granular casts, and in the fourth it was clear. In three cases the kidneys were about normal in size and color, and in the other three they were somewhat swollen. In two of the latter three cases the color was darker than normal and mottled, while in the other it was rather pale. In every case the capsule stripped easily.

The microscopie picture (Figs. 1, 2, and 3) was very similar in all the kidneys although the degree of change present was more marked in some. The glomerular tufts were dilated and completely filled the capsule in every case. Many of the glomeruli were apparently normal, but in each case there were some capsules which showed thickening and hyaline degeneration of the basement membrane, and some proliferation of the endothelial layer. There was distinct cystic formation of the glomerular capsules in five cases, and new formation

of elastic tissue around some of the glomeruli in one. There was more or less degeneration of the tubules in all, with atrophy of the epithelium and dilatation of the lumens in which were exudate and desquamated cells. The greater number of the tubules appeared normal, and the areas of degeneration which were present were more or less closely associated with the areas in which the glomeruli were most severely damaged. There were distinct areas of round-cell infiltration in every case, occurring chiefly near the larger veins at the inner margin of the cortex, but in two cases there was definite infiltration in the region of the damaged glomeruli. The greatest amount of tubular change was found associated with these areas of round-cell infiltration. In four of the cases there was no definite increase in the intertubular connective tissue, but in the other two there was definite fibrosis in the medullary rays which extended to the surface and corresponded with distinct though microscopic dimples on it. There was deposit of calcium salts in two cases.

These results would indicate that long-continued, mild intoxication with uranium nitrate will produce a beginning fibrosis in the kidneys. It would seem that the condition is progressive, and it is interesting to note that the animal which showed the greatest amount of fibrosis in the kidneys had received the greatest number of injections. The picture rather closely resembles that described by Weigert in subgroup 1 of the "chronic hemorrhagic with heart hypertrophy," and although I am unable to say that the animals' hearts were hypertrophied, I believe that the kidneys of this series may be classed under that heading.

In Series II the results obtained were just as constant and much more striking. Each injection was sufficiently strong to produce a definite subacute attack of nephritis from which the animal usually recovered. A glance at the charts, Figures 4 and 7, will give some idea of the results of each injection. In nearly all cases there was a definite albuminuria with more or less retention of the chlorids and phosphates. There was definite loss of weight after almost every injection. In two cases there was definite polyuria towards the end of the experiment, and similar comparison could not be made in two of the remaining cases because the animals had not been kept in the metabolism cages for a sufficiently long time. As stated above, I was unable to find casts in the twenty-four-hour samples of urine except on rare occasions, but in two of the four cases in which there was urine in the bladder after death, numerous granular casts were found, and in one of the other cases in which the urine was rich in albumin,

a microscopic examination was unfortunately not made. In only one case was the urine obtained in the bladder free from both albumin and casts. At autopsy only two of the animals had any fluid in the peritoneal cavity, but in four there were distinct macroscopic dimples in the cortex of the kidneys to which the capsule was adherent, and in one of these the kidneys were small, pale and distinctly granular.

The microscopic picture (Figs. 5 and 6) showed marked proliferation of the interstitial connective tissue with distinct dimpling of the surface of the kidney and marked tubular and glomerular destruction. In one case the new growth of fibrous tissue seemed to be more marked in the inner zone of the cortex, but in the other four it was quite diffuse, and in two cases it extended to the intertubular connective tissue in the medulla. The most striking feature was the advanced degree of glomerular change, a fact that is all the more remarkable when we remember that in the acute intoxication there was comparatively little involvement. The glomerular changes included thickening of the capsules with hyaline degeneration of the basement membranes and proliferation of the endothelium in every case, new formation of elastic tissue around some of the glomerular capsules in four cases, cystic formation in three cases, rather marked proliferation of the connective tissue of the tufts in two cases, and complete hyaline degeneration of a few of the tufts in one case. The convoluted tubules were severely damaged in four cases, and moderately so in one. There was marked atrophy and practical obliteration of many of the tubules, and dilatation with degeneration of the epithelium in many others. The dilated lumens of the latter contained exudate and desquamated cells. Many of the ascending limbs of Henle's loops were dilated and contained exudate and debris, and some of them were blocked by dense hyaline casts. The collecting tubules showed little damage to their epithelium but contained exudate and desquamated cells. The new-formed connective tissue was fairly rich in cells and there was round-cell infiltration in one case. The newly formed elastic tissue was found only around the damaged glomeruli outside the thickened basement membrane, and in some cases it seemed to be continuous with the elastic tissue in the walls of the small arteries. There was some deposit of calcium salts in the medulla in two cases, and rich deposit in both medulla and cortex in two cases.

The results obtained in this group show very definitely that following a series of subacute attacks of nephritis such as is produced by uranium nitrate there is marked and permanent damage to the kidneys. The marked increase in the interstitial tissue, the extreme

degree of tubular and glomerular change, and the occurrence of polyuria towards the end of the experiment, show a decided resemblance to the conditions found in chronic interstitial nephritis in man. Although I cannot say that the blood pressure was high, nor that there was definite hypertrophy of the left ventricle of the heart, yet the analogy to those conditions described by Weigert as the "most chronic" of the "chronic hemorrhagic with heart hypertrophy," is, I believe, sufficiently strong to justify a classification under that heading. Indeed in the one case (Guinea-pig 21), one might almost be justified in classing the kidneys as true secondary contracted or granular atrophic kidneys.

In Series III I can not draw comparisons as I have in Series I and II, because of the difference of the duration of the experiments, and because I have no complete records of the urine excretion during the experiments. There was, however, this in common, viz., that in every case the animal was so ill for several days after the injection that it was doubtful whether or not he would recover. I have already referred to protocols 1 and 2 in my discussion of the microscopic picture in acute poisoning by uranium nitrate. Guinea-pig 16 (Protocol 3) and Guinea-pig 15 (which also died on the seventh day, but which is not reported in detail), show already a beginning proliferation of the endothelium of the glomerular capsules and numerous areas of round-cell infiltration, although the most striking feature is that even this early there is definite cystic formation of the glomeruli and also of the tubules. In Guinea-pig 19 (Protocol 4), Fig. 8, there is a very marked cystic formation which is chiefly glomerular in origin, and in the left kidney, which is the least damaged, it is seen that the condition apparently commences in the inner zone of the cortex. This is of interest because we shall see that the two most severely damaged kidneys of this group also show this characteristic. There is rather marked though recent new-formed connective tissue between the tubules, and the fact that the condition is progressive is evidenced by the areas of round-cell infiltration. The glomeruli show beginning proliferation of the endothelium in a few cases, but there is no definite thickening of the capsule, and no hyaline degeneration of the basement membrane. This kidney is interesting in that it undoubtedly shows an early stage of the condition to which we shall refer later, and that it also shows how early we may find well-marked proliferation of the interstitial tissue, and advanced cystic dilatation of the glomerular capsules. Guinea-pigs 33 and 35 (Protocols 5 and 6), Figs. 9 and 10, furnish examples of the more advanced changes. Both show advanced fibrosis of the kidneys with marked tubular and glomerular changes, with

the formation of cysts, hyaline degeneration of the basement membranes, and new formation of elastic tissue around some of the glomeruli. In Guinea-pig 35 the change is almost entirely confined to the inner zone of the cortex, although there are some processes which extend to the surface and correspond to distinct depressions on it. In Guinea-pig 33, however, the condition is much more general, and although there is greater cystic degeneration of the glomeruli in the inner zone of the cortex, yet almost all the cortex has undergone extensive fibrotic change. In Protocols 7 and 8 we have changes which, although slight as compared with those in Guinea-pig 33, are nevertheless definitely of the nature of chronic lesions. There is cyst formation and rather extensive glomerular thickening, but there is no general increase in the intertubular connective tissue.

A review of this series cannot fail to show that the lesions described in Protocols 4, 5, and 6 must be closely related; and the rather marked cystic change described in Protocol 3 would indicate that this must also be included. The results show definitely that following a single severe attack of parenchymatous nephritis, such as is produced by uranium nitrate, there may be severe and permanent damage to the kidneys which may go on so far as to result in the production of a granular, atrophic kidney. Protocols 5 and 6 show this most distinctly, and I think that Protocol 4 may also be included as showing an earlier stage of what must undoubtedly have resulted in a condition similar to that described in Protocol 5. The findings in Protocols 7 and 8 would indicate that in other cases, although there may be a certain number of permanent chronic lesions produced in the kidneys, there must be a remarkable tendency to recuperation even after exceedingly severe attacks of acute parenchymatous nephritis.

The most striking feature in these three series is the extreme degree of glomerular change which is found in the kidneys that show chronic lesions. As I noted above, this is all the more remarkable when we remember the insignificant amount of damage to the glomeruli which is found in the acute intoxication with this drug. In Series I there is the possibility that the condition is due to the long-continued mild irritation of the repeated small doses, but in Series II and III this cannot be the explanation. In these two series the change is undoubtedly secondary to the damage done by the acute poisoning, and in this it bears out Senator's teaching that the whole tube system is damaged as a result of injury to any part of the system. Ponfick<sup>22</sup> believes that

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22. Ponfick: Ueber Morbus Brightii (Referat). Verhandl. d. deutsch. path. Gesellsch., 1905, ix, 49.

such a condition may be the result of a passive process in which the glomerulus becomes atrophied through disuse because of a prolonged plugging of the tubule by a dense hyaline cast. Müller,<sup>4</sup> on the other hand, suggests that it may be a non-progressive fibrosis due to scar formation, in which the scar is the result of the injury to the parenchyma by the primary acute attack. In my series, however, there is a quite constant feature which it may be well to mention, as it may tend to support Senator's theory<sup>2</sup> that the secondary contracted kidney is the result of a progressive process because of some damage to the vascular system. In all the advanced cases of Series III, in four of the five cases in Series II, and in one case in Series I, new-formed elastic tissue fibers were found around some of the damaged glomeruli. Melnikow-Ruswedenkow<sup>23</sup> has described this condition in a series of diseased human kidneys in which he found the elastic tissue around the glomerular capsules, outside the thickened basement membrane. (In my cases it was invariably in this situation that the new-formed elastic tissue was found. See Fig. 6. In some instances in which it was found in a scar near the surface of the kidney, the elastic fibers seemed to be derived from the elastic tissue in the capsule of the kidney, but in all other cases the origin was in the walls of the blood vessels. He says definitely that its occurrence depends on the vascular system, that it may be present in either general or local circulatory disturbances, and that Bowman's capsule is the most frequent seat because it stands in such intimate relation to the walls of the arterial branches. Hohenemser<sup>24</sup> demonstrated the presence of newly formed elastic fibers in the kidney tissue in seventeen cases of arteriosclerotic and chronic inflammatory kidneys. He says that it occurs only in the region of, and in closest dependence upon the blood vessels, and that in common the amount of elastic tissue present stands in direct relation to the amount of shrinkage of the organ affected. Now in view of these explanations as to the origin of the new formed elastic tissue in the kidney (which, by the way, are all the references on the subject that I was able to find in the literature at my disposal), if we consider also that in Series III the lesions appeared to commence and to be more severe in the inner zone of the cortex which is near to the large blood vessels, and that in all my cases of acute poisoning which showed round-cell infiltration, and in many of the cases in Series I. the areas of round-cell infiltration seemed to be in the neighborhood

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23. Melnikow-Ruswedenkow: *Histologische Untersuchungen über die elastische Gewebe in normalen und in pathologische veränderten Organen*. Beitr. z. path. Anat. n. g. allg. Path. (Ziegler's), xxvi, 564.

24. Hohenemser: *Ueber der Vorkommen von elastischen Fasern bei cirrhotischen Prozessen d. Lebers und Niere*. Virchow's Arch. f. path. Anat., cxl, 192.



of the larger vessels, it may be that uranium nitrate causes some damage to the vascular system which so far we have been unable to demonstrate, and it may be that it is this vascular disturbance which is responsible for the secondary glomerular and tubular destruction. It is interesting to note in this connection that Heineke and Meyerstein<sup>25</sup> concluded from their observations on acute uranium poisoning that there must be some vascular change because of the occurrence of severe edema in cases in which there was very little renal damage.<sup>26</sup>

It is not my intention to try to explain the results obtained. I feel that perhaps I should apologize for suggesting a classification for the types described in Series I and II, but I make that classification merely to emphasize the very close resemblance which exists between the lesions produced by uranium nitrate poisoning and those which are found in the various types of subacute and chronic diffuse nephritis in man. I believe I have demonstrated beyond question that it is possible to produce in animals conditions which closely resemble those found in subacute and chronic interstitial nephritis in man, and that during the development of these conditions I have in certain cases been able to demonstrate characteristic urinary findings.

#### CONCLUSIONS

1. By the use of uranium nitrate it is possible to produce in animals lesions which closely resemble those found in subacute and chronic diffuse nephritis in man.

2. A long-continued mild intoxication with this drug will lead to the production of a "subchronic" (Weigert) interstitial nephritis which would appear to be progressive.

3. A series of several attacks of subacute uranium nephritis will lead to extensive fibrotic changes in the kidney which in some cases goes on to the stage of a granular atrophy. In a certain number of cases this condition is associated with the condition of polyuria.

4. A single severe attack of acute parenchymatous nephritis may be followed after some weeks by a more or less severe fibrosis, which in some cases goes on to extreme granular atrophy. In other cases, however, the recuperative power of the kidney is such that only a moderate fibrosis results.

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25. Heineke and Meyerstein: Experimentelle Untersuchungen über die Hydrops bei Nierenkrankheiten. *Deutsch. Arch. f. klin. Med.*, 1907, *xv*, 101.

26. It may be of interest to mention here that in one guinea-pig, No. 26, and in one rabbit (out of two injected), distinct plaques of intimal and medial thickening were found in the aorta near the aortic valves. The number is too small to draw any conclusions as the lesions may have been spontaneous, but careful examination will be made of the aorta in all our future cases.

## THE TREPONEMA PALLIDUM

OBSERVATIONS ON ITS OCCURRENCE AND DEMONSTRATION IN SYPHILITIC LESIONS\*

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The discovery by Schaudinn and Hoffmann<sup>1</sup> in 1905 of a spirillum in various luetic lesions marked the beginning of a decided advance in our knowledge of the etiology of syphilis. The announcement of the discovery, while most conservative in its assertions, gave a fresh impetus to the study of the many phases presented in the parasitology and pathology of this disease. A wide-spread interest was awakened and many investigators directed their attention to the problems in this new field of research. From the results of many of their observations we have already gained a new conception of the cause, course and treatment of lues.

The organism found by Schaudinn and Hoffmann was first described by them under the name of *Spirochæta pallida*, but a more intimate study of its morphology led them to forsake its classification under the spirochætæ and to rename it the *Treponema pallidum*. Much careful study has been given to the biologic nature of this organism, its demonstration and its behavior toward staining reagents. No less attention has been directed to observations on its occurrence in specific and non-specific lesions, and to the effect produced by both local and general treatment on its presence in such lesions. The evidence thus far available seems to show that this spirillum differs in its characteristics from all other known spirilla and thus probably constitutes a new species. Its absence from non-specific lesions and its almost constant presence in specific lesions are being demonstrated repeatedly, while its general disappearance from these lesions under local and systemic treatment is an observation reported from many sides. These facts adduced from such evidence would seem to establish this organism as the actual infecting agent in syphilis. Owing

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1. Schaudinn and Hoffmann: Vorläufiger Bericht über das Vorkommen von Spirochæten in syphilitischen Krankheitsprodukten und bei Papillomen. Arb. a. d. k. Gsundtsamte, 1905, xxii, 527.—Ueber *Spirocharta pallida* bei Syphilis und die Unterschiede dieser Form gegenüber anderen Arten dieser Gattung. Berliklin. Wehnsehr., 1905, No. 42, p. 673.

to the fact, however, that the *Treponema* fulfils only one of the conditions of Koch's law—since, so far, all attempts to cultivate it have proved futile—we can make no definite statement concerning the specificity of its rôle.

Although this further confirmation is lacking, yet in the clinics and among the private practitioners in Europe, and to a small but increasing extent in this country, the presence of the *Treponema* in a suspected lesion is held as establishing the specific nature of the infection, and therefore its demonstration in such cases is considered as a valuable diagnostic aid. With the older methods of observation, on the other hand, often a delay of several weeks was necessary, depending on the appearance of secondary symptoms, before a definite diagnosis could be made. An early diagnosis is now asserted to be of distinct advantage in the treatment of this disease.

#### I.—THE DEMONSTRATION OF THE TREPONEMA

The inaccessibility of much of the literature, combined with the more or less unsatisfactory results obtained with the intricate and time-consuming staining methods, may account for the lack of initiative on the part of many of the medical men of this country to avail themselves of this aid to diagnosis. It is therefore the purpose of this paper to give a critical review of the various methods recommended for staining the *Treponema*, to describe a simple and reliable procedure for its demonstration, and, further, to report a series of observations made in about one hundred cases, both syphilitic and non-syphilitic in character.

As a diagnostic measure, the recovery and demonstration of the *Treponema pallidum* from primary lesions is probably of greatest importance, and in this instance the attempt usually meets with a greater degree of success than is the case when later lesions are examined. Its presence in some of the secondary lesions is frequently less constant and its demonstration presents greater difficulties. Reports of positive findings in the pustules and ulcers of the tertiary stage are comparatively few in number. The recovery of the spirillum from the circulating blood in primary and secondary syphilis has been reported, but the nature of the technic renders any description unnecessary here.

The untreated chancre, the condylomata, the mucous patches and moist papules offer the most promising field for investigation, but the precise nature of the material to be obtained from these lesions is of primary importance. Many failures to demonstrate the *Treponema* are traceable to the faulty manner of preparing the specimen rather than

to the method of staining employed. Some authors advise that a small incision be made in the lesion with a lance or a Hagedorn needle, and the resulting drop of blood spread in a thin film on a cover glass or slide. This method is not always feasible or satisfactory. The method used in the present research is simple in execution and produces uniform and dependable results. Since this step constitutes so important a factor in making a successful preparation its detailed description may be justified here:

The lesion is washed when necessary, then thoroughly cleansed by wiping with gauze. The juncture of the necrotic with the sound tissue, and also a part of the floor of the sore, are then curetted with a small curette (the chalazion eye curette answers the purpose admirably), or scraped with a scalpel until the detritus and superficial tissue are removed and a slight flow of blood is produced. The lesion is then sponged with dry gauze until the blood has ceased to flow and clear serum is seen to ooze. A drop of this serum is then spread on a perfectly clean glass slide in the thinnest possible uniform film. The preparation, after being allowed to dry in the air, may be fixed either by carefully passing through the flame three times, by immersion in ethyl or methyl alcohol, by osmic acid or in the osmium tube of Hamm.

The inability of early investigators to demonstrate the existence of the *Treponema* in syphilitic lesions may be ascribed in part to the inadequacy of the optical appliances then available and to the difficulties presented in impregnating its cell substance with any of the usual staining reagents. The perfecting of apparatus for the production of dark-ground illumination has made it possible to render these poorly refracting cell bodies visible, and to enable one to observe them in a living condition. This method of direct examination is by far the most satisfactory, not only for making a rapid diagnosis of suspected material, but for an intimate study of the morphology and manner of reproduction of these organisms. The employment of this method is, however, limited by the nature of the apparatus required.<sup>2</sup>

The simplest, and for general purposes, the most satisfactory method of demonstrating the *Treponema* is, therefore, by means of some appropriate staining procedure. Such a vast array of staining methods has been advocated that a search for one which involves no elaborate technic, which is rapid in execution and which gives satisfactory preparations leads only to bewilderment. A great majority of these

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2. Recently this method has been described in detail by Harris and Corbus: The clinical value of the spirochæta pallida in the diagnosis and treatment of syphilis. Jour. Am. Med. Assn., 1908, li, 1928.

methods, when attempted by one not skilled in laboratory manipulations, yield discouraging results, and this means of diagnosis is then abandoned or intrusted to those who have given more or less study to the technic involved.

The difficulty in demonstrating the syphilis organism by any of the usual laboratory methods is largely due to the fact that the protoplasm of the *Treponema* exhibits only a slight affinity for the majority of the anilin stains. Schaudinn and Hoffmann<sup>1</sup> were the first to succeed in producing stained preparations of these spirilla. They found that in smears, fixed with osmic acid and allowed to remain immersed in Giemsa solution for twenty-four hours, the *Treponema* acquired a delicate rose color, while other spirilla which might be confused with the *Treponema* were more intensely stained. Since the publication of this method, the Giemsa solution, particularly the preparation of Grüber, has been widely employed for this purpose. Many modifications in its use have been advocated, each being supported by claims as possessing distinct advantages over the original procedure. For the most part these variations yield no more satisfactory results than the method of Schaudinn and Hoffmann. One modification, however, that described by Schereschewsky,<sup>3</sup> is so simple in detail and produces such excellent results that it has been almost exclusively employed in the present investigation. This method will be fully described in another part of this paper.

When it was learned that a demonstrable micro-organism was present in the lesions of syphilis many bacteriologists resorted to the common staining reagents in the hope of discovering a method which would render the use of the more delicate eosin and azure solutions unnecessary. Methylene blue, either in watery or alcoholic solution or prepared according to the method of Loeffler, has been employed by Borrel and Burnet,<sup>4</sup> Weitlaner<sup>5</sup> and others who have found that it renders the *Treponema* visible and imparts to it a distinct blue color. Others, among them, Bandi and Simonelli,<sup>6</sup> Ehrlich and Lenartowicz<sup>7</sup>

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3. Schereschewsky: Das Verhalten der *Spirochæta pallida* (Schaudinn) bei der Giemsa-Färbung. Centralbl. f. Bakteriöl., 1908, No. 45, p. 91.

4. Borrel and Burnet: Procédé de diagnostic rapide des lésions syphilitiques, Compt. rend. Soc. de biol., 1906, No. 49, 212.

5. Weitlaner: Noch einiges über *Spirochæta pallida*. Klin. therap. Wehnschr., Vienna, 1905, No. 12, p. 1124.

6. Bandi and Simonelli: Ueber die Anwesenheit der *Spirochæta pallida* in sekundär-syphilitischen Manifestationen und über die zu ihrem Nachweis angewendeten Färbungsmethoden. München. med. Wehnschr., 1905, No. 52, 1668.

7. Ehrlich and Lenartowicz: Ueber Färbungen der *Spirochæta pallida* für diagnostische Zwecke. Wien. med. Wehnschr., 1908, No. 58, p. 1018.

have obtained satisfactory results with Ziehl's solution of carbol fuchsin, while Gonder and Hoffmann, Ploeger,<sup>8</sup> Herxheimer,<sup>9</sup> Oppenheimer and Sachs,<sup>10</sup> and Scholtz<sup>11</sup> advocate the use of gentian violet in a solution of anilin water, or better in dilute carbolic acid. The intensity of the stain produced by the various anilins seems to be markedly increased by the use of phenol, either in dilute solution as a solvent for the stain or in combination with other substances as a mordant. Proca and Vasilescu<sup>12</sup> first mordant the preparation with a solution of tannic acid in 5 per cent. carbolic acid and then stain with carbol gentian violet. Flexner<sup>13</sup> has reported favorable results obtained with this method.

Quite different from any of the above methods is that described by Stern.<sup>14</sup> The air-dried film is fixed by heating at a temperature of 37.5 C. for several hours. The slide is then immersed in a colorless glass vessel containing a 10 per cent. watery solution of silver nitrate. The vessel is allowed to stand in diffuse daylight until the film appears brown with a metallic luster. If the action of the light has not been too intense, after thoroughly washing in water, the *Treponema* should appear evenly stained a deep brown with little precipitate on the slide. Flexner<sup>13</sup> advises that the reduction be allowed to take place slowly in weakly diffuse light, as otherwise the protoplasm appears coarse and the contour is more or less broken and uneven. With this stain the cell body is somewhat swollen and does not show the delicate appearance produced by eosin-azure stains. This has little significance from a diagnostic standpoint, as none of the other characteristics are affected. This method has been repeatedly tried in this laboratory and has given positive results when it was impossible to demonstrate the presence of the *Treponema* with many of the other stains. The *Treponema* impregnated by the above method is shown in *b-b* in the accompanying illustration.

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8. Ploeger: Die Spirochäten bei Syphilis. München. med. Wehnsehr., 1905, No. 52, p. 1381.

9. Herxheimer: Zur Kenntnis der *Spirochæta pallida*. München. med. Wehnsehr., 1905, No. 52, p. 1861.

10. Oppenheim and Sachs: Eine einfache und schnelle Methode zur deutlichen Darstellung der *Spirochæta pallida*. Deutsch. med. Wehnsehr., 1905, No. 31, p. 1156.

11. Scholz: Ueber den Spirochätennachweis bei Syphilis. Deutsch. med. Wehnsehr., 1905, No. 31, p. 1467.

12. Proca and Vasilescu: Sur un procédé de coloration rapide du *Spirochæta pallida*. Compt rend. Soc. de biol., 1905, No. 57, p. 1044.

13. Flexner: *Spirochæta (Treponema) pallida* and syphilis. Jour. Exper. Med., 1907, No. 9, p. 464.

14. Stern: Ueber den Nachweis der *Spirochæta pallida* im Ausstrich mittelst der Silbermethode. Berl. klin. Wehnsehr., 1907, No. 44, p. 400.

In this laboratory all of the above mentioned methods, and further those advocated by Goldhorn,<sup>15</sup> Wood, Hastings,<sup>16</sup> and Gradle<sup>17</sup> have been thoroughly tried out on material known to contain the Treponema in large numbers. In addition to the testing of these methods original attempts were also made to stain this organism with certain anilin colors, among them thionin, pyronin, safrinin and the three-solution diphtheria stain of Neisser. To summarize briefly the present observations made on the respective merits of these various methods it may be stated that: (a) of the simple anilin colors, fuchsine, methylene blue and gentian violet, when they do not yield entirely negative results, impregnate the protoplasm of the Treponema only to a slight degree; (b) the action of these anilins is intensified by the use of phenol or tannin as mordants, but at the best their employment leads to unsatisfactory preparations; (c) the silver impregnation method of Stern is thoroughly dependable, but the length of time required for its execution constitutes more or less of a disadvantage; (d) the Treponema is stained more intensely by solutions containing eosin and azure; (e) the Giemsa solution as used by Schaudinn and Hoffmann, and in many of its later modifications, may usually be depended on to produce well stained preparations, but with its employment are associated certain unsatisfactory features in the matter of time consumption, etc.

The results obtained by the method as modified by Schereschewsky have proven uniformly satisfactory. This fact, combined with its rapidity of execution and simplicity of technique, has led to its adoption in preference to all others for the purposes of the present investigation. The technique in detail is as follows:

The smears are obtained in the manner already described and after being allowed to dry in the air are carefully passed through the flame three times. The staining mixture is freshly prepared by adding thirteen drops (from a dropping bottle) of Giemsa solution (Grübler) to 10 c.c. of a 0.5 per cent. watery glycerin solution. The mixture is then heated to boiling, immediately poured on the slide and allowed to remain for three to five minutes. The stain is then poured off and the slide washed with neutral distilled water. The slide is dried by rapidly shaking it in the air and a second application is made for the same length of time. As a rule two applications suffice to impart to the

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15. Goldhorn: A rapid and certain method of staining *Spirochæta pallida*. Proc. New York Path. Soc., 1905, No. 5, 169.

16. This stain has recently been recommended by Geraghty: Johns Hopkins Hosp. Bull., 1908, XIX, 364.

17. Gradle (H. S.): A clinical stain for the *Spirochæta pallida*. Jour. Am. Med. Assn., 1908, 1, 1265.

smear a distinct pinkish tinge. Should the pink be too faint a third application is made. When the desired shade is reached the slide is washed as above and dried by shaking or with fine blotting paper. The preparation is then examined with a one-twelfth oil-immersion lens. In order to obtain ideal results certain precautions must be heeded. All vessels with which the stain comes in contact must be perfectly clean. Before mixing each fresh lot of stain the test tube used should be cleansed by scrubbing with clean cotton and alcohol, then rinsed with distilled water. Any deposit of stain about the neck and lip of the dropping bottle should be removed by carefully wiping with filter paper. The water used in making the glycerin solution and for washing the slide should be neutral, as the least degree of acidity causes the formation of a precipitate. Should any of these precautions be neglected it will be found that a heavy bluish precipitate forms in the mixture on boiling and its staining ability is thus impaired. The exact tint of the smear to be attained is a matter of no great importance and is easily determined. After a few trials in which the importance of the above details is realized one may expect to produce satisfactory preparations.

In the preparations thus stained the *Treponema* should appear a deep pink with the background pale in comparison. Fixation by heat has a tendency to straighten the convolutions, but this may be easily overcome with the exercise of a little care. The Schereschewsky stain, on account of the glycerin it contains, produces a slight swelling of the cell body. With this stain, however, a sufficiently accurate exposition of the morphologic features of the *Treponema* is produced. The *Treponema pallidum* is a delicate spirillum varying in length from 4 to 14 microns, and having a breadth which is generally less than 0.25 microns. The ends are somewhat pointed. The convolutions, according to Hoffmann and Halle,<sup>18</sup> have a width of 1 to 1.2 microns, a depth of 1 to 1.5 microns, and are usually 6 to 14 in number, although at times longer forms are seen which exhibit as many as 20 to 24 convolutions. The angularity and the regularity of these windings are markedly characteristic of this particular organism. A careful microscopic examination renders the differentiation of the *Treponema* from all other spirilla certain. The majority of spirochetes, on account of their coarser form, their irregular and broader convolutions and their greater affinity for stains, can scarcely be confused with the syphilis spirochete. The *Spirochaeta refringens*, frequently found in suspicious lesions, is

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18. Hoffman and Halle: Ueber eine bessere Darstellungsart der *Spirochaeta pallida* im Ausstrich. München med. Wehnschr., 1906, No. 53, p. 1516.



easily distinguished by its greater width and its more wavy form. Should doubt arise concerning the specific nature of the organism under examination the material should be examined in the fresh state best by means of the dark field illumination. When this is impossible the preparation may be fixed rapidly with osmic acid and then stained for several hours—preferably twenty-four—with a mixture containing one drop of the Giemsa solution in 10 c.c. of neutral distilled water. In all of the examinations made in this laboratory no difficulty has been experienced in establishing a diagnosis by means of the Sehereschewsky method.

## II.—THE OCCURRENCE OF THE *TREPONEMA* IN SYPHILITIC LESIONS<sup>19</sup>

It seems unnecessary to review here the large number of reported observations on the occurrence of the *Treponema* in syphilitic lesions. The results of these observations may be briefly summarized thus:

1. The *Treponema* has been found in the great majority of untreated primary and secondary lesions. Negative findings in such specific lesions are probably attributable to faulty technique.

2. The examination of material from tertiary lesions usually yields negative results. A few positive findings have been reported, however.

3. The *Treponema* has not been found in non-specific lesions.

4. Both local and general mercurial treatment tend first to make these spirochetes degenerate and later to cause their disappearance from the lesion.

With a view toward gaining further evidence in this direction a series of observations on 101 cases were made extending over a period of one year. A certain routine procedure was established which consisted in obtaining the material from the various lesions directly upon the admission of the patient to the clinic.<sup>20</sup> In many instances subsequent smears were made in order to verify the initial findings and without exception these were substantiated. Before publishing the results of these observations the appearance of the secondary symptoms was awaited—when the examination was made on the primary lesion—so

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19. A review of the literature extending through the year 1906 may be found in Kolle-Wassermann's *Handbuch der pathogenen Organismen*, Supplementary Volume I, 544; also in Mutzer: *Arch. f. Dermat. u. Syph.*, 1906, lxxix.

20. We wish to express here our sincere thanks to Doctors Pedersen, States and other members of the staff of the Genito-Urinary Clinic of the House of Relief, New York City, and to Doctors Morton, Read and others of the Genito-Urinary Clinic of the Polhemus Memorial Clinic, Brooklyn, N. Y., for their many courtesies and hearty cooperation.

that no doubt might exist concerning the specific nature of the case. These results may perhaps be best exhibited in tabular form.

The findings in the cases of untreated primary lesions are confirmatory of the results of others regarding the presence of the *Treponema* solely in specific lesions. Local treatment with the various preparations of mercury, such as calomel powder, blue ointment and black-

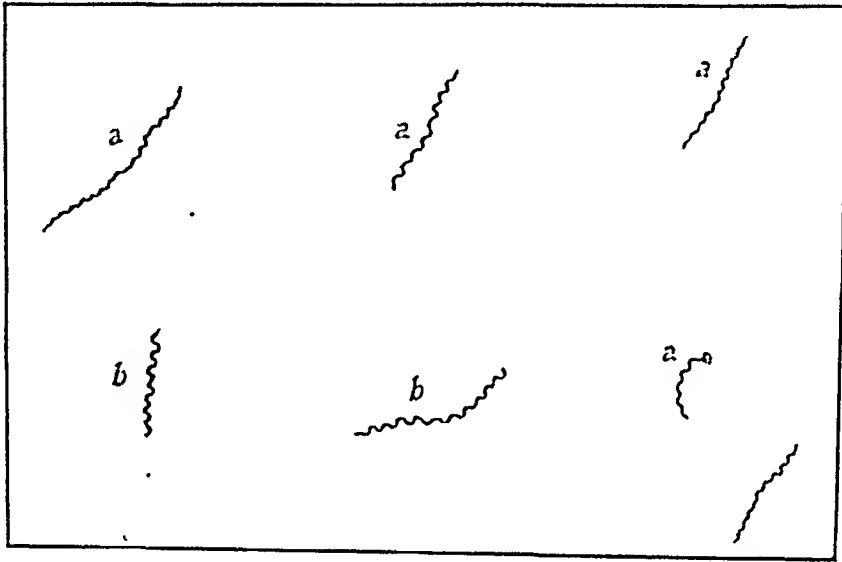
FINDINGS OF THE *TREPONEMA PALLIDUM* IN SPECIFIC AND NON-SPECIFIC LESIONS\*

Nature of Lesion.	Total Cases.	Positive Findings.	Negative Findings.	Per cent. Positive Findings.
Primary lesions, untreated . . . . .	33	33	0	100
Primary lesions, local treatment . . . . .	13	7	6	53
Primary lesions, general treatment . . . . .	1	0	1	00
Secondary lesions, untreated—				
Macular syphiloderms . . . . .	1	0	1	00
Maculopapular syphiloderms . . . . .	1	1	0	100
Condylomata . . . . .	3	3	0	100
Mucous patches . . . . .	1	1	0	100
Moist papules . . . . .	3	3	0	100
Secondary lesions, treated—				
Maculopapular syphiloderms . . . . .	3	1	2	33
Pustular syphiloderms . . . . .	2	0	2	00
Mucous patches . . . . .	6	3	3	50
Moist papules . . . . .	1	1	0	100
Tertiary lesions . . . . .	3	0	3	00
Non-specific lesions . . . . .	30	0	30	00

\* These results agree closely with the observations of Harris and Corbus (Jour. Am. Med. Assn., 1908, li, 1928), which have appeared since the completion of this paper and also with those of Geraghty (Johns Hopkins Hosp. Bull., 1908, xix, 364).

wash, may cause a disappearance of the *Treponema* from the superficial tissues, although it undoubtedly persists for a time in the deeper lymphatics of the lesions. Preparations made from mucous patches and moist papules, with the exception of three cases affected by treatment, were found to be unusually rich in spirochetes. Some of the prepara-

tions were taken directly from the surface of the lesion without previous enretting. This substantiates the earlier view of the highly infective nature of these particular lesions. The greater proportion of negative results in the secondary lesions after general treatment as compared to those before this treatment is indicative of the effects of the systemic administration of mercury on the presence of the *Treponema*. The absence of the *Treponema* in the cases of tertiary syphilis, while being in agreement with previous findings and with the usually accepted idea concerning the non-infective nature of these lesions, might be explained by some fault in our present method of examination.



*Treponema pallidum*, under magnification  $\times 1200$ ; *a-a* were stained with the Schereschewsky stain; *b-b* with the Stern silver stain.

From the review of the staining methods above recorded and from the observations made in the bacteriologic examination of syphilitic and non-syphilitic lesions the following conclusions may be reached:

1. The staining method as described by Schereschewsky appears to be the most satisfactory one for general use.

2. The presence of the *Treponema pallidum* in a suspected lesion may undoubtedly be considered as establishing the specific nature of the infection.

3. A negative result does not necessarily exclude the presence of syphilis. In this event further examinations should be made, and, when these lead to negative results a proper period of time should be allowed

to elapse in order that the appearance of the secondary symptoms may establish the diagnosis.

In the clinic of the House of Relief the finding of the *Treponema* has been considered as affording a positive diagnosis. The treatment when begun immediately on the report of a positive bacteriologic diagnosis has led to most gratifying results.

## THE PRODUCTION OF EDEMA

AN EXPERIMENTAL STUDY OF THE RELATIVE ETIOLOGIC IMPORTANCE OF  
RENAL INJURY, VASCULAR INJURY AND PLETHORIC HYDREMIA \*

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The investigation here presented had for its object the demonstration of the relative importance of vascular injury, renal injury and hydremia in the production of edema, and was suggested by a recent theoretical consideration<sup>1</sup> of the part played by chemical correlation in the pathologic conditions associated with disturbances of renal function.

Experimental evidence indicating the importance of hydremia or of vascular injury is not lacking, but, as it is based mainly on transfusion experiments, in which large amounts of fluid were used, and frequently experiments on dead or nephrectomized animals, it is not entirely satisfactory in that the conditions are too artificial. The recent observations on the edema of uranium nephritis point the way to a method of study which affords conditions more nearly in keeping with those associated with edema in man.

Uranium nephritis, in rabbits at least, is accompanied, when an excess of water is administered by the stomach-tube, as first shown by Richter,<sup>2</sup> by a well-marked edema of the subcutaneous tissues and by hydrops of the pleural and peritoneal cavities—a condition which several investigators have found not to occur when an excess of water is administered to animals poisoned with chromic salts, aoin and other renal irritants. This difference in effect would indicate that uranium nitrate has an action not common to the other renal poisons, and from our knowledge of edema it seems probable that this action is one injurious to the blood vessels. Of greater interest is the observation that the serum of an animal with uranium nephritis, when introduced into an animal with a chromate nephritis, causes the development of a well-

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\*This work, aided by a grant from the Rockefeller Institute for Medical Research, was begun in the Bender Laboratory, Albany, N. Y., and completed in the Carnegie Laboratory of The University and Bellevue Hospital Medical College.

1. Pearce (R. M.): The theory of chemical correlation as applied to the pathology of the kidney. *THE ARCHIVES INT. MED.*, 1908, ii, 77.

2. Richter (P. F.): Die experimentelle Erzeugung von Hydrops bei Nephritis, *Beitr. z. klin. Med. (Festschrift f. Senator)*, Hirschwald, Berlin, 1904; Experimentelles über die Nierenwassersucht. *Berl. klin. Wchnschr.*, 1905, xlii, 384.

marked edema. This phenomenon, first observed by Heineke<sup>3</sup> and since confirmed by Blanck,<sup>4</sup> who, however, finds it to be not a constant occurrence, suggests that in the serum of animals with nephritis there may occur substances which operate to produce edema. Two explanations seem possible: either the retention, as the result of kidney insufficiency, of substances which act as lymphagogues of the second order; or the injurious action on the endothelium of some substance or substances causing an alteration in its permeability to fluids. These several observations, therefore, suggest a new method of experimentation for determining the relative importance of hydremia, renal injury and vascular injury in the production of edema.

It is unnecessary, on account of the recent admirable presentation of the subject by Meltzer,<sup>5</sup> to go in detail into the question of the mechanistic *versus* the vitalistic theories of lymph formation. It is sufficient to recall that of the latter theories Heidenhain's, as well as Hamburger's, assumes an increased activity of the endothelial cells caused by katabolic products, and that Lazarus-Barlow and Asher believe in the influence of cell action, but of the cells of the organ rather than of the endothelia. Lazarus-Barlow further emphasizes the influence of waste products. Starling, who supports the purely physical theory, assumes an altered permeability of the endothelial membrane.

In connection with these theories of the physiology of lymph secretion, we have certain views concerning the pathologic secretion of lymph which point to vascular injury as an important factor. Cohnheim and Lichtheim,<sup>6</sup> in their well-known experiments on the production of hydremic plethora, found that the injection of large quantities of salt solution into the veins of rabbits and dogs, although it led to ascites and edema of the internal organs, did not cause edema of the normal skin and subcutaneous tissues; but if the skin was irritated, as by exposure to the sun, painting with iodine or immersion in hot water, local edema of the skin always followed transfusion. From these experiments Cohnheim concludes that the mild irritation of the skin caused an alteration of the capillary walls which made them more permeable for the fluid of the hydremic plethora. Support of this theory is offered by the experi-

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3. Heineke, quoted by Müller (F.): *Verhandl. d. deutsch. path. Gesellsch.*, 1905, ix, 64.

4. Blanck (S.): *Experimentelle Beiträge zur Pathogenese des Nierenwassersucht*, *Ztschr. f. klin. Med.*, 1906, ix, 572.

5. Meltzer (S. J.): *Edema*. *Am. Med.*, 1904, iii, 19, 59, 151, 191.

6. Cohnheim (J.) and Lichtheim (L.): *Ueber Hydrämie und hydrämisches Oedem*. *Virchow's Arch. f. path. Anat.*, 1877, lxi, 106.

ments of Magnus,<sup>7</sup> who finds that edema of the skin occurs in transfused animals if previously arsenic, which pharmacologists consider a specific poison for blood vessels, is injected, or if animals are in deep anesthesia from chloroform or ether. Magnus also finds that in nephrectomized animals transfusion leads to anasarca. Somewhat similar results have been obtained by Albu.<sup>8</sup> Closely related to Colnheim's theory of renal edema is that of Senator.<sup>9</sup> The difference is that Colnheim assumes that the altered permeability of the capillary walls is due to the action on these structures of toxic substances not eliminated as the result of renal insufficiency. Senator assumes that the edema is as much primary as is the renal lesion, and that the two are caused by the same toxic agent affecting the glomeruli of the kidney as well as the vessels of the skin, the toxic agent having its origin in the primary disease, as scarlet fever, malaria or other conditions.

The edema-producing power of the serum of nephritis has been only recently studied, and the observations are few in number. Heineke's experience with the serum of uraemic animals has been mentioned. This serum, from animals with edema, injected into animals poisoned with chromic salts, which, in Heineke's experience, does not cause edema, produced hydrops of the pleural and peritoneal cavities. His experiments were not reported in detail, but have been confirmed by Blanek, who, however, found that the condition could not be reproduced constantly.

In a later study with Meyerstein,<sup>10</sup> Heineke reports the production of edema in 64 per cent. of the animals receiving uraemic serum intravenously; but he also found edema in 60 per cent. of those receiving normal rabbit serum. The animals of both groups had been poisoned for four to five days with sodium bichromate and had received water and sodium chloride by the stomach-tube. As this treatment, in the absence of serum injection, did not cause edema, it is suggested that the serum in both instances had some injurious effect on the blood vessels. Of similar import are the results obtained by Georgopoulos,<sup>11</sup> who pro-

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7. Magnus (R.): Ueber die Entstehung der Hautödeme bei experimentelles hydrämischer Plethora. *Arch. f. exper. Path. u. Pharmak.*, 1899, xlii, 250.

8. Albu: Zur experimentellen Erzeugung von Oedemen and Hydropsien. *Virchow's Arch. f. path. Anat.*, 1901, clxvi, 87.

9. Senator (H.): Ueber die Wassersucht bei Nierenkrankheiten. *Berl. klin. Wehnschr.*, 1895, xxxiii, 165.

10. Heineke (A.) and Meyerstein (W.): Experimentelle Untersuchungen über den Hydrops bei Nierenkrankheiten. *Deutsch. Arch. f. klin. Med.*, 1907, xe, 101.

11. Georgopoulos: Experimentelle Beiträge zur Frage der Nierenwassersucht. *Ztschr. f. klin. Med.*, 1906, lx, 411.

duced a moderate edema by injecting nephrectomized rabbits with the serum of animals suffering with uranium nephritis.

In this connection should also be mentioned the observations of Kast<sup>12</sup> and Starling<sup>13</sup> on the lymphagogic action of the serum of edematous nephritics when injected into animals. Kast injected into the vein of a dog 75 cubic centimeters of the serum of a very edematous individual suffering from chronic hemorrhagic nephritis and found the flow of lymph to be increased tenfold. Sera from two other nephritics with edema increased the flow threefold and twofold, respectively, while the serum of normal individuals and of nephritics without edema gave no results, as was also the case in one instance, each, of uremia and cardiac dropsy. Starling reports a single experiment on the dog in which it was observed that the serum of a uremic individual caused a marked quickening of the flow of lymph from the thoracic duct.

My own experiments have had for their object the production, in the presence of artificial plethoric hydremia,<sup>14</sup> of edema by the administration of substances which would not only produce a renal lesion, but also injure the vessels of the body generally; but more especially the object has been to demonstrate ultimately the presence of endotheliotoxic substances in the serum of animals with experimental nephritis.

Experiments covering only the first part of this proposition are here presented. Rabbits have been treated with substances known to be both renal and vascular poisons, and hydremia has been produced by introducing through a stomach-tube a considerable amount of water. In other experiments a specific renal poison has been administered first, and later a vascular poison, or *vice versa*. The substances used have been potassium chromate, uranium nitrate, arsenious acid, ricin and snake venom. To these are added some very suggestive experiments with nephrotoxic immune serum which appear to indicate that this serum has definite endotheliotoxic properties.

The influence of salt retention as a factor has not been lost sight of, but no attempt has been made to determine the effect of the increased

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12. Kast (A.): Ueber lymphagoge Stoffe im Blutserum Nierenkranken. Deutsch. Arch. f. klin. Med., 1902, lxxiii, 562.

13. Starling (E. H.): Physiologic factors involved in the causation of dropsy. Lancet, London, 1896, cl, 1407.

14. This term, "plethoric hydremia," is used to indicate an increase in the amount of water in the circulating fluid, without necessarily a decrease of the proteid constituents. The term "hydremia" is hardly appropriate, as it was originally used to indicate a dilute condition of the blood resulting from the withdrawal of protein by albuminuria. Wherever, therefore, the term "hydremia" is used in this paper it refers to condition of plethora due to increased ingestion of fluid.



administration of this substance. As primary salt retention has not been proved, it has been assumed that salt retention accompanies water retention and that, therefore, this factor would be constant in all experiments.

That this plan of study represents a somewhat crude way of approaching the problem is at once acknowledged. It seemed to me, however, that, by adopting a careful system of controls, information of value might be possibly obtained.

#### 1. EXPERIMENTS WITH URANIUM NITRATE

The first experiments had for their object the confirmation of the observations of Richter and others, that edema is associated, when an excess of water is administered, with the nephritis caused by uranium nitrate. Such confirmation was readily obtained, as is shown in the following experiment.

*Rabbit 13*, weight 1,830 grams, on Jan. 30, 1908, and February 1 received 0.0075 grams uranium nitrate subcutaneously; on January 31 and February 1 and 2, 100 cubic centimeters of water were administered by stomach-tube. Albumin appeared in the urine on January 31 and increased in amount rapidly until February 3, when no urine was voided. On that date the animal was killed.

The examination showed well-marked edema of the subcutaneous tissues, about 15 cubic centimeters of clear fluid in the abdominal cavity and smaller amounts in each pleural cavity. The subpleural, subperitoneal and perirenal tissues were distinctly edematous. Especially noteworthy was the edema of the kidneys and their pelvis and ureters. The latter were greatly swollen and on cross-section presented a uniform glistening, gelatinous appearance, with apparently complete obliteration of their lumina. The bladder contained only 3 cubic centimeters of urine; microscopically this urine showed an abundance of fine granular casts, a few hyaline casts and leucocytes and epithelial cells.

In definite contrast to this is the absence of edema in animals receiving uranium, but no water; for example, the following:

*Rabbit 36*, weighing 2,410 grams, received on March 23, 24 and 25, 1908, 1 cubic centimeter of uranium subcutaneously. Albumin was present in the urine on March 24 and 25 and anuria developed on the 26th; the animal died on the 27th. No increase of fluid in either tissues or cavities of the body was found on postmortem examination.

Although similar negative results were obtained in four other animals thus treated, it must be admitted that Georgopoulos found varying grades of edema in three animals receiving uranium nitrate, but no water.

These experiments bring out the well-known relation of kidney injury and hydremia in the production of edema, but the relation of vascular injury is not so clear, though it is possible the latter was present and due to uranium nitrate. That this salt has an injurious effect on vascular structures is generally assumed, though it must be admitted

that the evidence on this point is not conclusive, being a matter of opinion rather than of actual observation.<sup>15</sup> Leaving this question for the present, we may turn to the experiments in which definite vascular poisons were used.

## II. EXPERIMENTS WITH ARSENIC

Arsenic, which pharmacologists consider a vascular as well as a renal poison, was employed in the early experiments. Nine rabbits were used; all received daily 0.5 to 1 cubic centimeter of a 1 per cent. solution of arsenious acid; six of these received also 50 to 100 cubic centimeters of water by the stomach-tube daily, and into the subcutaneous tissues of three of the latter potassium chromate was injected previous to the arsenic.

The animals receiving arsenic alone developed a localized edema at points of injection, but nowhere else. The following protocol illustrates this experiment:

*Rabbit 44*, weighing 1,700 grams, received, on March 25, 26, 27 and 28, 1908, 1 cubic centimeter of a 1 per cent. solution of arsenious acid subcutaneously. The urine contained only faint traces of albumin. No urine was voided on the 28th and 29th, and on the latter date the animal was killed. About the areas of injection and closely limited to these points the subcutaneous tissues were infiltrated with a slightly blood-tinged fluid which gave a gelatinous appearance. The peritoneal and pleural cavity contained no fluid. The bladder contained 5 cubic centimeters of thick urine which responded to tests for albumin.

The three rabbits receiving water by the stomach, in addition to arsenic subcutaneously, presented diffuse edema of varying grades, the most severe of which may be described as follows:

*Rabbit 43*, weighing 2,080 grams, received 1 cubic centimeter of arsenic solution subcutaneously and 100 cubic centimeters of water by stomach on March 25, 26, 27 and 28, 1908. Albumin appeared in the urine on the 27th; the 29th, when the animal died, no urine was voided. The subcutaneous tissues of the entire abdomen presented a diffuse edematous condition, with here and there petechial hemorrhages. The edema was not limited to points of injection but involved subcutaneous tissues of nether portion of body and extended into all four legs. Ten cubic centimeters of clear fluid were present in the peritoneal cavity and three in each pleural cavity. The bladder contained no urine.

The other two animals, in which anuria did not develop, presented a frank, but less extensive edema.

In the third group of three animals a chromate nephritis was first produced and then arsenic and water administered. The resulting edema was of about the same extent as in those receiving arsenic and water.

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15. The recent observations of Schlayer, Hedinger and Takayasu (Ueber nephritisches Oedem, Deutsch. Arch. f. klin. Med., 1907, xci, 59) indicate that the lesions of uranium nephritis include an increased permeability of the cutaneous vessels following a decreased permeability of the glomerular vessels.

The first of these three groups of experiments illustrates a local edema, due to direct vascular injury, and the second and third the influence of hydremia, and presumably the greater diffusion of the vascular poison, in causing a general edema. In the third group, although two renal poisons were administered, the edema did not differ from that of the second group. This would indicate that possibly arsenic does not add to the lesion caused by the chrome salt, or that the degree of kidney injury is relatively unimportant.

### III. EXPERIMENTS WITH RICIN AND VENOM

Of special importance are the experiments in which ricin or venom was administered to rabbits with chromate nephritis and artificial hydremia. Neither ricin or venom has the power, except in large or rapidly repeated doses, of producing serious injury to the kidney. On the other hand, ricin has been found by several investigators to cause very severe vascular injury. This is brought out very prominently in Flexner's<sup>16</sup> study of the lesions caused by this substance. Venom (*Crotalus adamanteus*) also seriously injures blood vessels, and, as shown by Flexner and Noguchi,<sup>17</sup> contains an endotheliolytic substance which these investigators termed "hemorrhagin." It was the influence of this endotheliolytic substance that was especially sought in the experiments with venom. Both substances, but especially venom, have a variety of toxic effects, but any possible influence which these may have on the production of edema I have attempted to control.

The rattlesnake venom used was obtained from Dr. Hideyo Noguchi, of the Rockefeller Institute, and the ricin from Prof. C. H. Bunting, of the University of Wisconsin, to both of whom I am greatly indebted, in that I was thus able without preliminary testing to use preparations the toxicity of which they had determined.

The chief experiments were very completely controlled by other experiments in which animals received (1) ricin alone, (2) water alone, (3) ricin and water, (4) potassium chromate alone, (5) potassium chromate and water, (6) potassium chromate and ricin. A similar set of controls was made with venom.

In each of four sets of experiments with ricin and four with venom this scheme was followed. In this way the results in the chief experiments were satisfactorily controlled by the other combinations. The

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16. Flexner (S.): The pathology of toxalbumin intoxication. Johns Hopkins Hosp. Rep., 1897, vi, 346.

17. Flexner (S.) and Noguchi (H.): The constitution of snake venom and snake sera. Univ. Penn. Med. Bull., 1902, xv, 345.

animals of the major experiments, receiving ricin (or venom), chrome and water, usually died on the fifth or sixth day; the others, for the sake of comparison, were killed at the same time. The ricin and venom were injected into the ear vein, the former in doses of 0.02 mg., the latter of 0.5 mg. of the dried venom on the first, second and fifth days. The potassium chromate was given subcutaneously in doses of 0.03 gram on the first and second days. Water, usually 100 cubic centimeters, was administered daily by stomach-tube. In some experiments this regularity in the administration of the chromate solution or the venom and ricin was varied.

Three of the four animals receiving ricin, potassium chromate and water developed a severe and widespread edema, as is seen in the following protocol. The fourth, dying on the third day, had an edema of less degree, with only a very small amount of fluid in the serous cavities.

*Rabbit 104*, weighing 1,695 grams, was isolated on Jan. 10, 1909. The urine of the 11th was normal and the animal received 0.02 mg. ricin in the ear vein, 0.03 gram potassium chromate subcutaneously, and 100 cubic centimeters of water by stomach-tube. This treatment was repeated on January 12 and again on the 15th. On the 13th, 14th and 16th water only was given. The urine of the 12th contained a trace of albumin and that of the succeeding days showed a severe albuminuria. Casts were abundant. Anuria did not develop and the animal was killed on the 17th. At the autopsy was found a well-marked edema of the subcutaneous tissues of the abdomen and thorax, 24 c.c. of fluid in the abdominal cavity and 16 c.c. in both pleural cavities. The retroperitoneal, perirenal and pelvic fat and tissue about the pancreas presented an extreme edema of characteristic gelatinous appearance; a similar condition existed in the retrosternal and mediastinal tissues.

In a second animal of this group, the subcutaneous tissues of the abdomen were swollen to a thickness of 0.8 cm. and the serous fluid dripped freely from the incision. The edema of the skin of this animal was so extreme that the hair could be readily scraped from considerable areas.

Similar results were obtained with animals receiving venom. In one animal, dying on the third day, the edema was limited to the subcutaneous tissue, but in the other three, living five or six days, it was of the general type shown in the following experiment:

*Rabbit 103*, weighing 2,230 grams, was isolated on Jan. 10, 1909. On the following day the urine was found to be normal and the animal received 0.5 mg. venom in the ear vein, 0.03 gram potassium chromate subcutaneously, and 100 cubic centimeters of water by stomach-tube. This treatment was repeated on January 12 and 15, with the administration of water only on the 13th and 14th. Albumin in small amount was found in the urine of the 12th and in large amounts on succeeding days; casts were abundant; no anuria. Death occurred on the morning of the 16th. Postmortem examination showed a moderate but very diffuse hemorrhagic edema of the subcutaneous tissues of abdomen and thorax, great distention of abdomen by ascites and 5 cubic centimeters of fluid in

each pleural cavity. The retroserous tissues generally, but especially retroperitoneal and mediastinal, were greatly distended by fluid. The pancreas lay in a gelatinous mass of edematous fat tissue. The ureters and pelvis of kidney showed a hemorrhagic edema which increased the cross-section of the upper ureter to a diameter of half a centimeter. A similar edema involved the perirenal fat. The kidney itself was edematous and had a peculiar mottled appearance due to extreme injection of the glomeruli. A few small hemorrhages were seen in the liver.

The control experiments follow:

1. *Ricin*.—This, given alone, causes no edema, though in two animals the peritoneal or pleural surfaces were unusually moist and barely 2 cubic centimeters of fluid could be drained from these cavities. No serious disturbance of the kidney occurs, though the urine occasionally contains a trace of albumin.

2. *Venom*.—After the administration of venom only, although ecchymotic hemorrhages are frequent, no edema has been found, except in one instance, in which a hemorrhagic edema of the ureters and pelves of kidneys occurred, with increased moisture of the serous membranes. The urine of this animal contained abundant albumin, numerous red blood corpuscles, and a few casts. In none of the other animals did the urine contain more than an occasional trace of albumin. Histologically, however, some of these kidneys showed exudative glomerular lesions, due apparently to the vascular injury caused by the venom.

3. *Water*.—The administration of water by the stomach-tube in daily amounts of 50, 75 or 100 cubic centimeters, according to the size of the animal, has not led to interstitial edema, though in two instances less than 3 cubic centimeters of clear fluid have been drained from the serous cavities of thorax and abdomen.

4. *Ricin and Water*.—In this series, in one animal 6 cubic centimeters of fluid were found in the abdominal cavity and 1 cubic centimeter in each of the pleural cavities. The other animals presented no evidence of edema. The moderate escape of fluid seen in one of these animals may represent a slight grade of the very extensive ascites which Flexner describes as the result of injecting intravenously large doses (0.1 to 3 mg.) of ricin and which also caused serious lesions of the kidney.

5. *Venom and Water*.—The results here, with the exception of one experiment, did not differ from those with venom only. The exception presents, however, one of the most marked examples of edema which has been met in the entire investigation and will be presented in detail.

*Rabbit 102*, weighing 1,590 grams, was isolated on Jan. 10, 1909. On January 11 its urine was found free of albumin and it received in the ear vein 0.5 mg. of venom and by stomach-tube, 100 cubic centimeters of water, which treatment was repeated on the 12th. On January 13 and 14 water only was given. On January

12 the urine was free of albumin, but on the 13th it was reddish in color and by the spectroscope was found to contain hemoglobin; albumin was present in considerable amount and the sediment contained numerous casts, red blood corpuscles and renal cells. No urine was passed on the 14th, and on the 15th, shortly after death, only a small amount, highly concentrated and containing a large amount of albumin; hematuria was still present. On postmortem examination was found a slight but readily demonstrable edema involving diffusely the subcutaneous tissues of the abdomen. The peritoneal cavity contained 24 cubic centimeters of bloody fluid and the pleural cavities about 10 each. The pelvis of both kidneys and first portion of both ureters were intensely edematous and hemorrhagic. The bladder contained 13 cubic centimeters of thick blood-tinged urine. Fat necroses were present in the abdominal fat generally and to less extent in that of pleura and pericardium with a few foci in the subcutaneous fat, especially that about the mammary glands. Microscopic examination of the kidney revealed a severe acute exudative glomerular nephritis.

Here was produced unexpectedly, as the result of a severe exudative nephritis due to the action of venom on the glomerular capillaries, the full picture of edema observed in animals receiving venom and water during a chromate nephritis. The essential element of kidney injury had been brought about in a peculiarly susceptible animal, and the control experiment became a major experiment, illustrating completely the thesis under consideration.

6. *Potassium Chromate*.—The subcutaneous injection of potassium chromate, in dose of 0.03 gm. daily for three days, produces a severe nephritis which the animal may survive, but which usually causes death in four to five days. Such animals present a definite gelatinous edema of the subcutaneous tissues immediately about the point of injection without tendency to become diffuse. No excess of fluid is found in the serous cavities. With animals receiving a single dose or two doses, and living a longer time, the result is the same.

6. *Potassium Chromate and Water*.—In this group the edema about point of injection was very definite and tended to involve the adjacent tissues to some extent. It did not, however, become diffuse, and in three of the animals no accumulations of fluid were found elsewhere. In a fourth, however, the abdominal cavity contained 4 and the pleural cavities 10 cubic centimeters of clear fluid and the retrosternal tissue showed a very definite edema. In the fifth animal of this series occurred an edema of such extent that it is deemed advisable to present the notes in full.

*Rabbit 100*, weighing 1,920 grams, was isolated on Jan. 10, 1909. The urine of the 11th was normal, and on this day the animal received 0.03 gram of potassium chromate subcutaneously and 100 c.c. of water by the stomach tube. The treatment was repeated on the 12th, and on the 13th, 14th and 15th water only was administered. Albumin appeared in the urine on the 12th and was present in large amounts on the 13th and 14th. No urine was voided on the 15th and until noon of the 16th, when the animal was killed by chloroform, the anuria

was complete. At autopsy was found a diffuse gelatinous edema of the subcutaneous tissues of the abdomen and thorax, which in some places measured a centimeter in thickness. Free fluid in considerable amounts could readily be squeezed from these tissues. The abdomen contained 11 cubic centimeters of clear fluid and the perirenal, retroperitoneal and pelvic fat, and that about the stomach and pancreas was distended as the result of an infiltration by a clear fluid, giving the tissues a jelly-like appearance. The pelves of the kidneys and the upper portion of the ureters were slightly edematous. Each pleural cavity contained a small amount of fluid and the retrosternal tissues were plainly edematous. The bladder contained only 4 cubic centimeters of urine.

Here, again, an experiment, planned as a control, differs from its fellows and becomes a positive experiment. The only possible explanation of vascular injury lies in the occurrence of anuria, which presumably allows the accumulation of non-eliminated substances capable of injuring vascular endothelium and causing edema.

8. *Potassium Chromate and Ricin*.—In these controls occurred a very intense edema at the point of injection of the chrome solution, and for a distance of several centimeters about this point, but not involving the abdomen generally and with no accumulation of fluid elsewhere in the body. The infiltration was, however, more extensive than that following chrome injections only, the result presumably of the added action of the ricin, on the blood vessels.

9. *Potassium Chromate and Venom*.—This combination caused a widespread hemorrhagic edema of the subcutaneous tissues of the abdomen encroaching in one animal on the thorax and in another extending to the tissues of the neck and proximal portions of extremities. In none, however, despite the presence of small hemorrhages of serous membranes, did fluid accumulate elsewhere.

These control experiments have been presented somewhat at length for two purposes: first, as fairly satisfactory controls of the preceding experiments, and, second, to illustrate some of the difficulties of controlling perfectly the three factors of plethoric hydremia, renal injury and vascular injury. It is evident that in most instances, with the doses here given, no one of these factors, or combination of two, is sufficient to produce a general condition which might be termed edema. Occasionally, however, it is difficult to interpret a small accumulation of fluid in one of the body cavities, and the value of the control is thus lessened. In this connection it is worthy of note that recently in laparotomies on a series of five rabbits with albumin-free urine I have twice observed the presence of a small amount of free fluid in the abdominal cavity. It is evident, therefore, that normal rabbits, under ether anesthesia at least, may occasionally present this condition. As has been seen, the third factor may at any time develop, as in Rabbit 102, in

which a severe nephritis unexpectedly complicated the experiment and led to a widespread condition of edema. Again, in Rabbit 100, an anuria, by allowing, presumably, the retention of products capable of vascular injury, was probably responsible for the unexpected edema.

It may also be pointed out that the various controls with chrome salts illustrate the circumscribed influence of a simple local injury. Chrome alone causes a purely local edema. When water is administered simultaneously, the edema is not so sharply circumscribed, but may still be considered as localized. When chrome and venom are given together, the involvement of the subcutaneous tissue, despite the absence of artificial hydremia, is very extensive, without, however, the occurrence of increased transudation elsewhere in the body.

From a comparison of the chief experiments and their controls it would appear justifiable to conclude that, for the production of general edema, the three factors—nephritis, vascular injury and an increase of the body fluids—are all essential. No one of these alone, and no combination of two, is sufficient. The frequent occurrence of anuria precludes the possibility of a true hydremia, due to a loss of albumin, being a factor. That cardiac insufficiency may play a part is suggested by the frequent occurrence of edema in dependent parts, but on this point I have been unable to reach a definite opinion.

*Nature of the Kidney Injury.*—In regard to the question of kidney injury, it has seemed advisable to investigate one phase of this influence; that is, whether the part played by nephritis in the production of edema is the result of a change in the character of the renal function or is due to a reduction of functional area. To determine this point, experiments have been made on ten animals, the kidney substance of which had been mechanically reduced by operation. From each the entire kidney and one-half (upper pole) of the left were removed under ether anesthesia according to the method described by Dr. Sampson<sup>18</sup> and myself. Treatment was begun, in order to forestall compensatory hyperplasia, on the day after the operation and was carried on as in the ricin and venom experiments, except that chromate solution was not given for the production of nephritis. Two animals received ricin and venom, respectively; two, water only; two, water and ricin; two, water and venom, and one, water and both ricin and venom. The last of these died on the fourth day, as did also one of those receiving water only (renal hemorrhage). Of the others, one died on the sixth day, and the rest were killed one

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18. Sampson (J. A.) and Pearce (R. M.): A study of experimental reduction of kidney tissue with special reference to the changes in that remaining. *Jour. Exper. Med.*, 1908, x, 745.



week after the operation. In none was there evidence of definite edema of the tissues or undue accumulation of fluid in the body cavities, although in the animal receiving venom only and in one of those receiving water only, the serous cavities were unusually moist and contained a few drops of free fluid.

The comparison of these experiments with those in which nephritis was produced indicates that the edema-producing effect of the nephritis is not to be explained by mere diminution of functional area.

#### IV. THE EFFECT OF NEPHROTOXIC IMMUNE SERUM

Heineke's observation, that the serum of uranium nephritis, when injected into a hydremic rabbit poisoned with chrome salts, had the power of causing edema, suggested a study of the influence of nephrotoxic immune serum. The result obtained by Heineke may be explained either by the action of substances which act as lymphagogues of the second order or by the injurious effect of some substance or substances acting on vascular endothelium and causing an alteration in the permeability to fluids. As such substances, developing in the course of nephritis, might be similar in nature to those of a nephrotoxic immune serum, which, as has been shown elsewhere,<sup>19</sup> has other properties than its influence on the kidney, such a serum was prepared. This was done by injecting into small dogs the washed kidneys of rabbits. The serum thus procured was injected into rabbits with chromate nephritis.

Preliminary control experiments were first made with normal dog serum. This was administered to two normal rabbits and to three rabbits with chromate nephritis, and at the same time an excess of water was given. In the normal rabbits no evidence of edema could be found. The following experiment is illustrative:

*Rabbit 20*, weighing 2,540 grams, received daily from Feb. 22 to 28, 1908, inclusive, 100 cubic centimeters of water by stomach tube, and on each of these days 5 to 20 cubic centimeters of normal dog serum, either subcutaneously or intraperitoneally. The animal was killed on the 29th. At autopsy no edema could be found.

Similar results were obtained when the serum was given in doses of 5 cubic centimeters daily in the ear vein.

In the second series of controls, with chromate rabbits, two showed only a local edema at site of the chromate injection. In the third occurred a very striking edema of the mucous membrane of the pelves of the kidneys, the ureters and the bladder.

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19. Pearce (R. M.): Concerning the specificity of the somatogenic cytotoxins. *Jour. Med. Research*, 1904, xxv, 576.

*Rabbit 31*, weighing 1,320 grams, received on March 16, 1908, 0.03 grams and on March 17 0.015 gram of potassium chromate; large amounts of albumin appeared in the urine after the first injection and persisted throughout the experiment. On March 16, 17, 18 and 19, 100 cubic centimeters of water were given by stomach-tube, and, on each of these days, 10 cubic centimeters of normal dog serum in the abdomen or the ear vein, alternately. The animal was killed on the 20th. Autopsy showed a well-marked edema of the mucosa and submucosa of the bladder, pelves of the kidneys and of the ureters, the latter being most markedly involved and appearing as solid gelatinous structures with no visible lumina. The retrosternal and peritracheal tissues were also slightly edematous, but no fluid was found in the cavities of the body and no edema of the subcutaneous tissues except very slight swellings at points of injection.

This very definitely localized edema was due apparently to the well-known toxic action of an alien serum affecting the vessels along the path of elimination, and it was hoped that this toxic action would be augmented by the nephrotoxic immune serum. Such a serum, as is now well known, is not specific in its action; in addition to its nephrotoxic power, it has also hemagglutinative and hemolytic properties, and affects, through these activities, the vessels of various organs. These latter properties were those most desired. Two of three animals receiving this serum developed a most extensive edema, while in the third it was localized to the neighborhood of the chromate injections. The following experiment illustrates the severe type:

*Rabbit 22*, weighing 1,480 grams, received on March 10 and 11, 1908, 0.03 gram potassium chromate subcutaneously. On each of the following three days the animal received 5 cubic centimeters of nephrotoxic immune serum in the abdominal cavity and 100 cubic centimeters of water by stomach-tube. The urine, from the 11th on, contained large amounts of albumin and the animal died on the 14th. The autopsy showed a very marked subcutaneous edema over the entire abdomen and thorax which involved all four legs to the paws. The thoracic and abdominal cavities were about half full of clear fluid and the retrosternal and mediastinal tissues were edematous. The pericardial cavity contained an excess of fluid. The kidneys and their pelves and the ureters were greatly swollen by fluid, as were also the tissues about the spleen. The bladder contained no urine.

To control the action of the nephrotoxic serum in absence of chromate nephritis, this serum was injected into two normal rabbits, which received an excess of water, with no results, except a moderate but very definite edema of the retrosternal tissues and with, in one, a small amount of fluid in the pleural cavities. One of these experiments follows:

*Rabbit 25*, weighing 1,630 grams, was isolated on Mar. 9, 1908. The urine was free of albumin on March 10. On March 11 to 15 inclusive the animal received daily 5 cubic centimeters of nephrotoxic immune serum in the peritoneal cavity and 100 cubic centimeters of water in the stomach. On the 12th considerable albumin appeared in the urine and persisted throughout the experiment. The rabbit was killed on the 16th. A peculiar gelatinous edema of the retrosternal tissues was present but no edema of the subcutaneous tissues or accumulations of fluid in the cavities of the body.

From this group of experiments it is evident that, even in the presence of hydremia, the toxic power of normal dog serum is not sufficient to produce serious disturbance, but that in an animal with kidney insufficiency due to a chromate nephritis a definite edema occurs. A nephrotoxic immune serum, which causes serious kidney injury, gives a somewhat similar grade of edema in hydremic animals; but in neither is the edema as severe as in hydremic chromate animals receiving nephrotoxic immune serum. The influence of the latter combination shows the great importance of renal insufficiency; the kidney receives an injury from two different renal poisons, either of which alone is capable of causing a serious nephritis and which combined, in the presence of hydremia, cause an edema as severe as any noted in the course of this investigation.

In these experiments an action on the endothelium of the vessels can not be definitely proved, but from our knowledge of cytotoxic immune sera it is proper to assume that the nephrotoxic serum contains endotheliotoxic as well as hemagglutinative and hemolytic bodies and that these endotheliotoxic substances may have been responsible for the severe type of edema.

An attempt has been made, in connection with this last type of experiment to produce, by similar means, an edema in dogs, but without the administration of an excess of water. Nephrotoxic immune serum, as well as serum from animals with spontaneous and uranium nephritis, has been injected into dogs suffering from chromate nephritis. In these experiments the animal was allowed to drink water freely, but no water was given by stomach-tube. In none of six experiments was edema found.

#### CONCLUSIONS

In uranium nephritis the ease with which edema is produced when an excess of water is administered illustrates the importance of hydremia in the causation of edema. The influence of vascular injury is not very plain in the uranium experiments, but is conclusively shown in those in which ricin, venom and arsenic were administered in the course of a chromate nephritis; in all of these the influence of hydremia is also evident.

A consideration of all the results recorded appears to demonstrate conclusively that, under the conditions of these experiments, plethoric hydremia and vascular injury have equal value with nephritis in the production of edema, and that no one of these three factors acting alone, and no combination of two acting together, is sufficient to cause edema.

The experiments with nephrotoxic immune sera point to the possibility that substances, presumably endotheliotoxic and capable by vascular injury of aiding in the production of edema, may be contained in serum.

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## PROTEIN METABOLISM IN ADDISON'S DISEASE

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Although Addison's disease is one very closely connected with a gland which must have important functions regulating metabolism, since associated with tuberculosis of this organ are general weakness, loss in weight and a marked pigmentation of the skin and the mucous membranes, nevertheless the amount of chemical work which has been done in an attempt to throw light on the process is not large.

Those investigators who have taken up the cases from the point of view of protein metabolism have in the main contented themselves with a study of the nitrogen balance, and these observations have been extended further to a simultaneous determination of the effect of the administration of adrenal gland substance on the protein breakdown.

Even here the results are not uniform, for Senator<sup>1</sup> believes that the physiologic effect of the gland substance in case of Addison's disease is to lead to increase in body weight and appetite and to produce a retention of nitrogen, but a slight minus balance in calcium. Both Kaufmann<sup>2</sup> and Piekhardt<sup>3</sup> report increased nitrogen loss during the administration of the tablets, and to-day the use of the gland in the treatment of the condition has lapsed into disfavor.

Not all the cases of Addison's disease, however, show a loss of nitrogen, for in some it will be seen that nitrogen equilibrium may be maintained on a diet which is not only low in nitrogen, but much below the average in heat units. Marchetti and Stefanelli,<sup>4</sup> on account of the way some of the patients react with this low nitrogen and caloric diets, advance the idea that the oxidative capacity of the organism is lowered.

Some isolated observations that have been made on the urine in Addison's disease lead one to suspect that the nitrogen and carbon metabolism may be abnormal. Leva<sup>5</sup> reports the presence of acetic and formic acids in the urine, and taurocholic acid was also said to have been detected. Gerhardt and Reichardt also say that large amounts

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1. Senator: *Charité-Ann.*, 1898, xxiii, 287.

2. Kaufmann: *Zentralbl. f. Stoffwechs. u. Verdauungskr.*, 1901, ii, 173.

3. Piekhardt: *Berl. klin. Wchnschr.*, 1898, xxxv, 727.

4. Marchetti and Stefanelli: *Riv. crit. di clin. med.*, 1901, ii, 773.

5. Leva: *Virchow's Arch. f. path. Anat.*, 1898, cxxv, 35.

of fatty acids were found in the urine, and the observation regarding taurocholic acid has been confirmed by Jacoby<sup>6</sup> in what is admitted to be a doubtful case. Marchetti and Stefanelli and Maragliano lay considerable stress on the indicanuria, while Leva and Pickhardt, on what appear to be good grounds, criticize the view that indicanuria is a symptom due directly to disturbance of the adrenal function, and point out that the appearance of large amounts of indican in the urine is probably the effect of increased intestinal putrefaction, such as occurs in many cases with diarrhea, and diarrhea is common in this disease.

That the protein metabolism, especially the endogenous protein metabolism, is lower than usual is indicated by the estimations of Leva of the kreatinin output. This observer found the kreatinin distinctly lowered, while in a control case of icterus the excretion was normal.

With regard to the proportion in which the nitrogen and sulphur containing constituents of the urine are excreted, there is an absolute lack of information.

It is true that Varannini,<sup>7</sup> Marchetti and Stefanelli and Leva all give the results of urea and uric acid estimations, but the methods employed can not be used to determine what the influence of the condition is on the nitrogen metabolism, so that these results will not be taken up in detail.

#### REPORT OF CASE

The case we report was that of a patient in Bellevue Hospital, and for the privilege of the examination we are indebted to the courtesy of Dr. Alexander Lambert.

The abstract from the notes of the case is as follows:

*Patient.*—M. M. male, aged 50, native of Ireland. There was no family history; no cancer or rheumatism. The patient drank beer, but seldom whiskey. He denied venereal disease.

*History.*—The patient had had no illness up to four years before coming under observation. He had to give up work on account of weakness and shortness of breath; was unable to walk without frequent stops for breath; had attacks of dizziness, with flashes before the eyes. About this time he noted that his skin was getting dark. This was first observed on the hands and face; later on other parts of the body. About two years later, he noticed that his legs were swollen. He arose two or three times in the night to urinate. He often had attacks of palpitation, but no fainting. His appetite was always good; he never had any gastro-intestinal disturbance. For two years he had pain and stiffness of the limbs after exposure to wet and cold. His chief complaint was general weakness.

*Physical Examination.*—The patient had a large frame, was well nourished, anemic, but did not seem to be acutely ill. The face and the upper part

6. Jacoby. *Charité-Ann.*, 1898, xxiii, 287.

7. Varannini: *Clin. med. ital.*, 1902, xli, 40.

of the body were deeply pigmented, with lighter streaks over the upper part of the face and forehead. The thighs and legs were lighter in color. The eyes were equal and reactive; to light normal; conjunctiva very pale. The tongue was clean and moist; the dorsal surface showed patches of dark pigmentation. This pigmentation was also seen on the inner sides of the cheeks. The neck was thick, rounded and rigid.

Thorax: percussion, negative. Breath sounds, distant and indistinct. Posteriorly, crepitant rales over each base. Heart, not enlarged. Left border percussed 10 cm. to left of median line. Action fairly regular. Sounds clear. Systolic murmur heard best in the pulmonic area. Arteries thickened. Pulse small, low tension with quick upstroke.

Abdomen: liver and spleen not enlarged.

Extremities: slight clubbing of the fingers.

The patient was quite weak, and very anemic. His appetite was always very great. Except for weakness and great hunger, he complained of nothing.

TABLE 1.—BLOOD EXAMINATION

Date.	Hemoglobin.	Erythrocytes.	Leucoocytes.	Polymorpho-nuclear.	Small Lymphocytes.	Large Lymphocytes.	Mononuclear.	Eosinophiles.	Basophiles.
April 11 . .	15	1,410,000	5000						
April 17 . . .	14	1,520,000	2500*	44.5	20.5	8.5	5.0	20.5	1.5
April 20 . . . . .			4700†	47.0	19.3	10.5	4.3	19.3	0.0
April 25 . .	18	1,764,000	5400‡	49.5	24.7	5.7	4.2	11.2	4.2
May 2 . . .	17	1,604,000	2300	52.3	22.3	8.6	3.6	10.6	2.3
May 19 . . . . .			6600	57.0					

\* Normoblast.

† Normoblast (300 cells).

‡ Myelocyte (200 cells).

His bowels were very constipated until he was put on an oatmeal diet. The high eosinophile count which appears in the report on the blood findings remains unaccounted for. The stools were repeatedly examined for parasites and none found. Trichinosis was excluded by excising a piece of the pectoral muscle and examining for trichinae. None were found.

*Dynamometric Tests.*—As general weakness is considered an important feature of Addison's disease, several dynamometric tests were made on the patient during his stay in the hospital. The results are as follows: R. and L. hands. April 8, R. 29.3 K.; L. 22.6 K.; April 16, R. 33.8 K.; L. 31.6 K.; April 17, R. 38.4 K.; L. 27.1 K.; April 25, R. 29.3 K.; L. 22.6 K.

*Blood Pressure.*—The blood pressure readings with the Janeway sphygmomanometer gave the following: April 17, R. 142; L. 138; April 25, 155; May 1, R. 116; L. 122; May 8, R. 107, L. 110; April 11 (Erlanger), Systolic, 128, Diastolic 90.

During the examination the temperature was subnormal, varying between 96 and 98 degrees. The pulse rate was between 76 and 92, and the respiration 20-24. The Calmette reaction was tried on several occasions with negative results.

## HOSPITAL LABORATORY REPORTS

*Urine.*—April 4: Cloudy, amber; sp. gr. 1010; albumin, very faint trace; no sugar, few leucocytes, no casts, Cammidge's reaction absent.

*Feces.*—April 11: Light brown, semi-solid, normal odor, not fatty. Microscopic, few starch granules, many bacteria, no muscle fibers, no parasitic ova.

*Blood.*—See Table 1.

*Diet.*—For the purposes of an examination of his protein metabolism, the patient was put on a diet containing the following: Eggs, 280 grams; milk, 960 c. e.; sugar, 16 grams; white bread, 130 grams; butter, 20 grams; boiled rice, 480 grams; oatmeal boiled, 900 grams; tea, 480 c. e. As the diet varied slightly from day to day, the amount of nitrogen, fat and carbohydrate are

TABLE 2.—NITROGEN, FAT, CARBOHYDRATE AND CALORIC VALUE OF FOOD

Date.	Total Nitrogen.	Calories.	Fat.	Calories.	Carbo-hydrate.	Calories.	Total Calories.
April 29 . . . . .	16.01	410	95.8	890	293	1200	2500
April 30 . . . . .	15.51	398	88.9	825	277	1130	2353
May 1 . . . . .	15.51	398	88.1	820	277	1130	2353
May 2 . . . . .	15.51	398	89.8	835	277	1130	2368
May 3 . . . . .	15.51	398	88.9	825	277	1130	2358
May 4 . . . . .	15.51	398	88.9	825	277	1130	2358
May 5 . . . . .	15.02	385	91.4	840	246	1010	2235
May 6 . . . . .	14.22	364	84.3	785	236	968	2117
May 7 . . . . .	15.51	398	88.9	825	277	1130	2358

given in Table 2 with the individual and total heat units of the food. As the average weight of the patient was 72 kilos and the average caloric value of the food 2300 calories, the patient received on an average 32 calories per kilo.

The urines were collected in twenty-four hour periods, and the methods which have been used in the analysis have been given in the various papers of one of us.

*Nitrogen Balance.*—We were unfortunately unable to collect the feces quantitatively in this case, and thus are unable to give the nitrogen and sulphur balances. An examination of the difference between the nitrogen intake and the amount excreted in the urine leads one to believe that a minus balance of nitrogen was improbable. The total nitrogen intake during the period of experiment was 138.3 grams. Of this 97.6 grams were excreted through the urine. The patient's weight at the beginning of the experiment was 66.3 kilos and at the end 65.8 kilos, a net loss of 500 grams.



*Volume of Urine.*—As will be seen from the tables, exceptionally high volumes of urine are recorded, with a correspondingly low specific gravity. On one day only did the volume fall below 1500 c.c., and on two days over 2500 c.c. were passed. On the days on which the lower volumes were excreted there is a low nitrogen output. As the patient was exceedingly difficult to control it is possible, even with the care which was taken in watching him that some of the urine was lost. This is to a certain extent confirmed by the lower kreatinin elimination found on these days.

*Amid Nitrogen.*—On this fraction of the nitrogen we are inclined to lay some special stress as representing the desamidating capacity of the organism which appears to be at fault in some conditions of toxic character. The present case represents a type of disease in which desamidation has not suffered in the least. Comparing the ratios here obtained with those found in normal individ-

TABLE 3.—NITROGEN AND SULPHUR PARTITION IN ADDISON'S DISEASE.

Date Received.	Volume. C.c.	Specific Gravity.	Total Nitrogen. Gms.	Gross Urea. Nitrogen. Gms.	Amid Nitrogen. Gms.	Urea Nitrogen. Gms.	Kreatinin. Nitrogen. Gms.	Uric Acid. Nitrogen. Gms.	Rest Nitrogen. Gms.	Gr. Urea. Per cent.	Ammonia. Per cent.	Urea. Per cent.	Kreatinin. Per cent.
April 30, '08... . .	2045	1007	11.220	10.210	0.916	9.294	0.382	0.074	0.554	91.00	8.17	82.83	3.41
May 1, '08... . .	2170	1007	12.484	11.320	1.138	10.182	0.381	0.074	0.702	90.70	9.15	81.55	3.08
May 2, '08... . .	1890	1008	9.090	8.320	0.800	7.520	0.274	0.060	0.436	91.50	8.80	82.70	3.01
May 3, '08... . .	2510	1008	11.780	10.820	0.980	9.840	0.310	0.083	0.537	91.90	8.38	83.52	2.89
May 4, '08... . .	2530	1008	11.740	10.728	0.860	9.868	0.320	0.056	0.627	91.38	7.32	84.06	2.80
May 5, '08... . .	2280	1007	11.628	10.579	0.889	9.690	0.315	0.059	0.675	90.96	7.65	83.31	2.71
May 6, '08... . .	1800	1008	10.980	10.135	0.918	9.217	0.333	0.032	0.480	92.28	8.36	83.92	3.03
May 7, '08	1360	1010	8.230	7.655	0.691	6.964	0.258	0.018	0.299	93.00	8.40	84.60	3.13
May 8, '08	1930	1009	10.500	9.726	0.965	8.761	0.310	0.027	0.437	92.65	9.23	83.42	2.95

uals, it will be seen that the average, 91.7 per cent, is quite as high as that which is found in healthy persons (88.5 per cent Shaffer<sup>8</sup>) and ratios higher have only been found by Schondörff and by one of us in animals receiving a large amount of meat.

*Ammonia Nitrogen.*—Both relatively and absolutely compared with urines of normal individuals on a similar diet, the ammonia nitrogen is high. This is interesting in view of the fact that other investigators have drawn attention to the presence of unusual acid products in the urine. While these were not tested for in the present case, the fact that no acetone was found in any of the samples of urine tested probably excludes the presence of acetoacetic and beta-oxybutyric acids. Despite this fact, one must admit a very considerable

8. Shaffer: Am. Jour. Physiol., 1908, xxii, 445.

degree of acidosis, not dependent on the character of the food intake. We hope at some future time to take up the study of this interesting feature of the case.

*Urea Nitrogen.*—Although the ammonia ratio is so much beyond that found in normal individuals, the high amid nitrogen ratio allows the urea ratio still to be quite within normal limits. The average for the entire series of analysis is 83.3 per cent, while Shaffer found for a similar diet 84.3 per cent. His ammonia ratio was however 4.3 per cent against our 8.3 per cent.

*Kreatinin.*—As an index of the total endogenous metabolism, it was of considerable importance to determine what the output of kreatinin was. As will be seen from the comparison with the normal figures the kreatinin is low. The patient weighed 72 kilos. The average output of kreatinin nitrogen during the time of examination was 0.32 grams. Per kilo body weight this gives a "kreatinin nitrogen coefficient" of  $0.32 \div 72 = 4.4$ . Even with the highest output

TABLE 3.—NITROGEN AND SULPHUR PARTITION IN ADDISON'S DISEASE—Continued

d.	Uric Acid. Per cent.	Rest Nitrogen. Per cent.	Total Sulphur. Gms.	Total Sulphate. Gms.	Alk. Sulphate. Gms.	Ethereal Sulphate. Gms.	Neutral Sulphur. Gms.	Total Sulphate. Per cent.	Alk. Sulphate. Per cent.	Ethereal Sulphate. Per cent.	Neutral Sulphur. Per cent.	100 Total Sulphur. Total Nitrogen.	Phosphorus. Gms.	Chlorin.
'08.	0.70	5.29	1.022	0.866	0.807	0.059	0.156	84.80	79.00	5.80	15.20	9.1	1.000	0.4
'08. .	0.59	5.63	1.024	0.836	0.783	0.053	0.188	81.56	76.40	5.16	18.44	8.2	1.048	0.5
'08. .	0.66	4.83	0.783	0.578	0.536	0.042	0.155	78.85	73.13	5.72	21.15	8.1	0.760	0.5
'08. .	0.70	4.51	0.956	0.783	0.670	0.113	0.173	81.90	70.09	11.81	18.10	8.1	1.052	0.8
'08. .	0.48	5.34	1.017	0.853	0.736	0.117	0.164	83.84	72.40	11.44	16.16	8.6	0.971	0.3
'08. .	0.51	5.82	0.930	0.798	0.707	0.091	0.132	85.77	75.98	9.79	14.23	8.0	1.015	0.7
'08. .	0.30	4.39	0.967	0.817	0.751	0.066	0.150	84.53	77.64	6.89	15.47	8.8	0.945	0.3
'08. .	0.22	3.65	0.722	0.598	0.558	0.040	0.124	82.88	77.22	5.66	17.12	8.8	0.851	0.3
'08. .	0.26	4.14	0.917	0.737	0.658	0.079	0.179	80.42	71.80	8.62	19.58	8.7	1.044	0.3

ines acid. No kreatin. No acetone.

kreatinin nitrogen, viz., 0.384 grams, the coefficient is still considerably below that which Shaffer considers normal. The coefficient in Shaffer's normal cases ranges from 11.7 to 5.4. Hence, in Addison's disease, a condition usually associated with a considerable degree of muscular weakness, the coefficient, as one might be led to expect from Shaffer's results, is low, and compares with what this observer found in diabetes and similar affections.

*Kreatin.*—The question of the presence or absence of kreatin from the urine has seemed to one of us from results which he has obtained to be of very considerable pathologic importance. Its presence in the urine is associated by some investigators invariably with loss of body protein, although this is assuredly not always the case. Others attribute its excretion to an impaired function of the liver. In any case, its appearance in the urine, when the factor

of starvation can be successfully eliminated, is probably of pathologic significance. In this case, as will be seen from the tables, kreatin is absent from the urine, and in the experience of one of us, it is the first important disease, associated with general weakness, in which no kreatin has been found. More information regarding the behavior of other cases of Addison's disease in this particular is earnestly desired.

*Uric Acid Nitrogen.*—On comparison with the data obtained from normal subjects, the uric acid nitrogen appears to be distinctly low, and this is especially the case towards the end of the experiment, when on one day only 0.018 grams were excreted. As an index of endogenous metabolism this corresponds with what was found in the kreatinin excretion. It is worthy of note that the low uric acid excretion is found on that day on which the lowest kreatinin output was observed. These results do not correspond with those of Marchetti and Stefanelli, who obtained on some days as much as a gram of uric acid, corresponding roughly to 0.3 grams of uric acid nitrogen.

*Rest Nitrogen.*—The absolute amount of rest nitrogen corresponds closely with what has been found in normal urines. The ratio moreover is not only within the normal limits, but is even below the values usually obtained.

#### THE PARTITION OF SULPHUR

*Total Sulphur.*—The impression which one obtains from an examination of the excretion of total sulphur is that it is high, and this is confirmed when one considers the relation which this component of the urine bears to the total nitrogen output. Shaffer's last determinations of the values in normal individuals give a ratio of 7.2. In this series of analyses the ratio is more than 1 per cent higher. While this is perhaps not of pathologic significance, one often sees in cases with the pathologic destruction of protein that apparently a type of protein is katabolized which is high in sulphur.

*Sulphate Sulphur.*—Comparing the results here obtained with those of Folin and Shaffer in normal subjects it will be seen that the oxidation of the sulphur part of the protein molecule has proceeded in every respect like that of a normal individual. There is certainly no deficiency in oxidation in so far as the sulphur group is concerned as has been asserted by the Italian investigators of this disease.

*Ethereal Sulphate Sulphur.*—In view of the importance which was at one time attached to the excretion of indican in Addison's disease it is interesting to examine the output of ethereal sulphur. The figures uniformly are somewhat high, especially on two days in the middle of the experiment, but an examination of the metabolites in normal individuals will disclose amounts of ethereal sulphur almost as high as those found here, so that one cannot assign to this any pathological importance.

*Neutral Sulphur.*—Neither relatively nor absolutely is the neutral sulphur increased above that found in normal subjects. As the sulphur of taurocholic acid would be found in this fraction, it is unlikely that the amount of taurocholic acid in these urines would be increased as some observers have claimed.

We are indebted to Mr. Emil Osterberg for much help in performing the chemical analyses described in this paper.

#### SUMMARY

The nitrogen and sulphur metabolism in a case of Addison's disease has been examined on a purin-free diet. The desamidating capacity of the patient and his capacity to transform the sulphur of the cystin

group into sulphuric acid were absolutely comparable to that of normal individuals. A considerable degree of acidosis was observed which is not accounted for by any factor which was found in this examination. The endogenous metabolism of the patient, as represented by the krea-  
tinin and uric acid outputs was below that of normal subjects.

## MILD UNCINARIA INFECTIONS

C. C. BASS, M.D.

NEW ORLEANS

Hookworm disease exists in a very large area of the civilized world, varying greatly in the extent of the infection in different localities. The Porto Rico Anemia Commission estimates that 90 per cent. of the population of Porto Rico are infected and that 30 per cent. of the deaths are due directly to this disease. No estimate can be placed on the number resulting from it indirectly. C. W. Stiles, who has especially directed attention to this disease in the southern states, has collected reports of many thousand cases all over the south. He is convinced that the death rate due directly thereto is very high, while that due indirectly to this disease is enormous. It is unnecessary to mention the importance of the economic side of the subject. The intensity of the infection varies greatly in different individuals.

It is intended to discuss in this paper briefly mild uncinaria infections (1) from the hygienic standpoint, (2) from the clinical side, and (3) to refer somewhat at length to certain manipulations in technic by which these cases can be more certainly recognized than by the ordinary examination of the feces.

### HYGIENIC CONSIDERATIONS

For every well-marked case of uncinariasis in the infected section of the southern states there are several patients having from one parasite up to a number sufficient to cause the ordinarily recognized symptoms. The proportion of mild to severe cases varies with the extent of the infection in a given locality, but it is perfectly consistent that there should be very few medium to severe cases in a given locality while yet a large percentage of the entire population may be infected to some extent. This is particularly likely to be true where there are many negroes. Negroes do not, as a rule, show marked symptoms, even when infected with many parasites. Those who have many eggs in the feces usually show only slight or no anemia if the blood is examined.

Many of the mild cases are those of persons who wear shoes and in whom there is no history or little probability of skin infection. Adults are likely to fall in this class. This argues the probability of mouth infection in this class of cases.

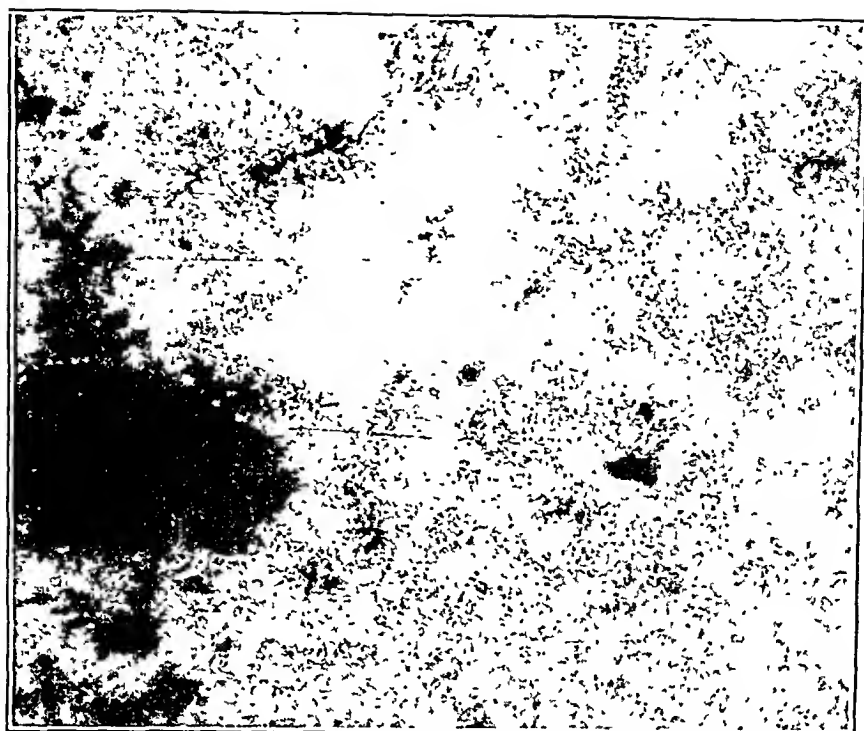


Fig. 1.—Photomicrographic view of feces containing uncinaria eggs. Only one egg is shown.

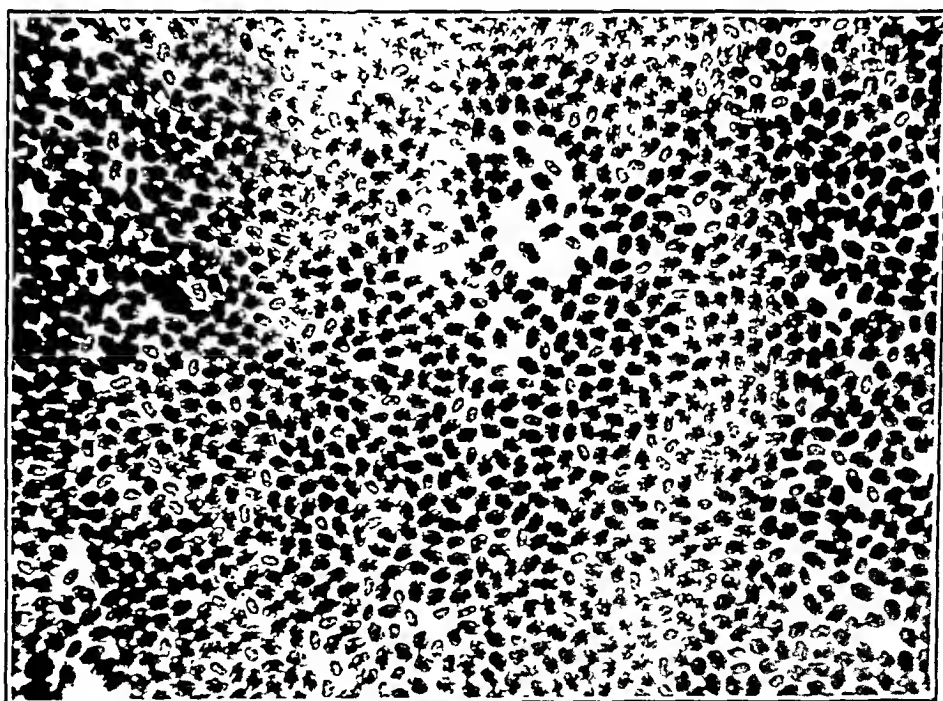


Fig. 2.—Eggs, practically free from fecal matter, obtained from specimen shown in Figure 1.

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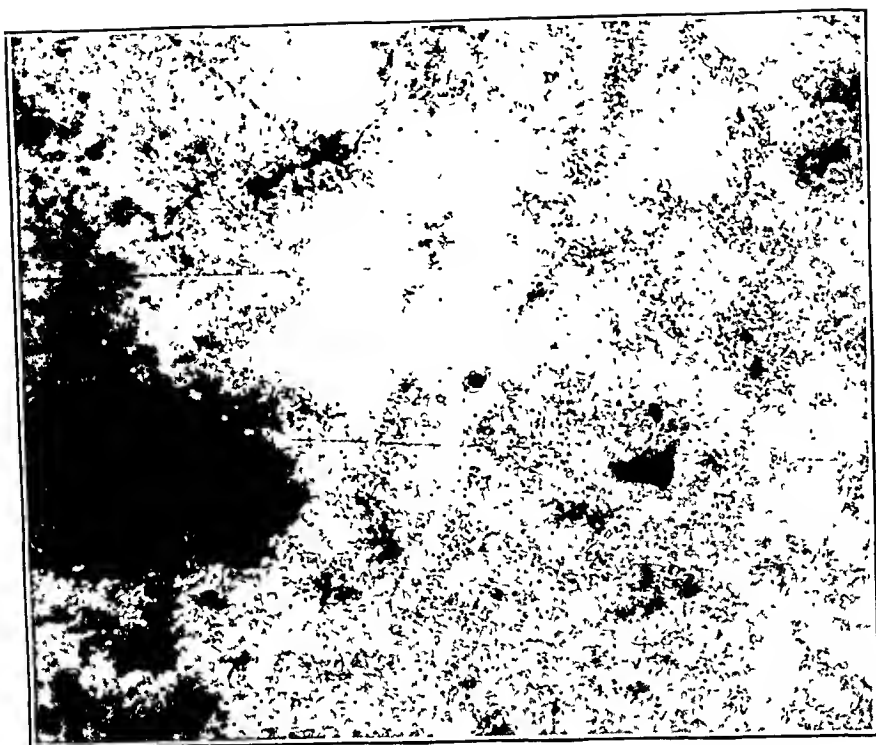


Fig. 1.—Photomicrographic view of feces containing uncinaria eggs. Only one is shown.

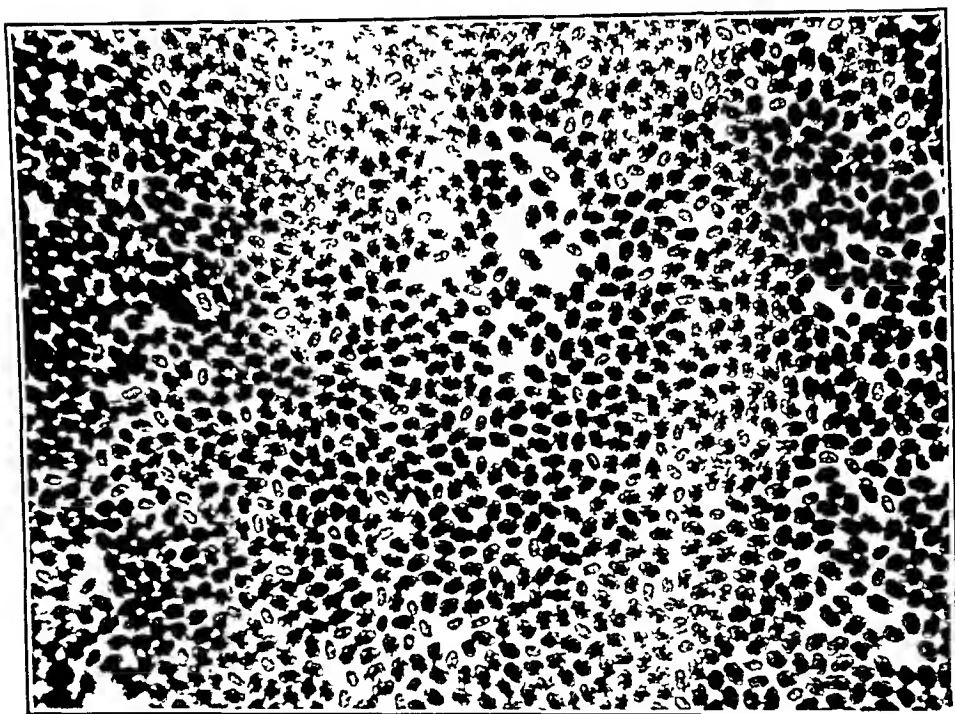


Fig. 2.—Eggs, practically free from fecal matter, obtained from specimen shown in Figure 1.



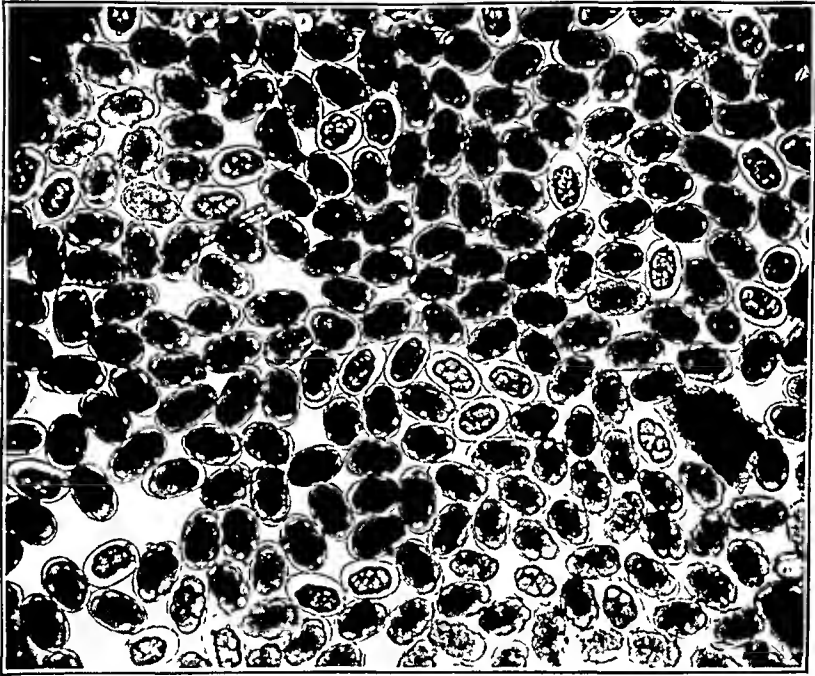


Fig. 3.—Higher-power view of eggs shown in Figure 2.

Mildly infected cases should be treated and warned against soil pollution, just as severer ones, for they may be a source of infection to others and give rise to severe cases. Just here the southern negro demands special consideration. His habits and bad hygiene include soil pollution, which, as shown by Stiles and others, is the great source of hookworm disease. The infected negro is a source of infection to others, while he himself enjoys considerable immunity from the effects of the parasite. He here plays the same rôle as he does in the spread of yellow fever, which he has in a mild and usually unrecognized form. His immunity from the effects of yellow-fever infection is illustrated by the experience at Tallulah, La., in 1905. The number of cases was: whites 80, with 18 deaths; colored about 950, deaths 5. Though there may not be the same difference in susceptibility to the effects of uncinaria infection, I am sure it is very considerable. Mildly infected patients and infected negroes compare well with the typhoid or diphtheria bacillus-carriers or the chronic malaria patients.

#### CLINICAL CONSIDERATIONS

The symptoms of uncinariasis are not always in proportion to the number of worms present. This no doubt is influenced largely by individual susceptibility and individual capacity of blood regeneration. It frequently happens that a patient with many worms has few or no symptoms, whereas another patient with few worms may have severe anemia or other symptoms. I am convinced, however, that those who have mild infections generally do not have recognizable symptoms.

Out of 152 cases of infection seen in which the symptoms were not sufficiently marked to attract special attention—cases which were, therefore, properly classed as mild—in only 26 per cent. was there more than 4 per cent. of eosinophiles, and in only 6 per cent. of the cases was there more than 6 per cent. of eosinophiles. Complete blood examination was made in 62 of these cases. The average percentage of hemoglobin was 90. The average number of red corpuscles was 5,125,000.

Of the 152 cases, 32 per cent. gave a history of more or less indigestion; 34 per cent. gave a history of pains and tenderness on pressure in the right side of the abdomen.

It is through the courtesy of Dr. J. B. Elliott, Sr., former professor of medicine in Tulane University, who was one of the first in our section to recognize the rôle of uncinariasis in producing a variety of vague digestive and abdominal symptoms, that I have seen several of these cases. The following cases are illustrative:

CASE 1.—J. B., aged 39, male, white, merchant, was well developed and looked fairly well; had never had ground itch; lived in town. He had had vague pains in the right side of abdomen as long as he could remember; said he was nervous and had "indigestion." Pains were not related to the time of eating. Physical examination failed to reveal anything abnormal. There were a few eggs in the stools; fourteen worms were recovered. The patient recovered entirely and gained nine pounds in nine weeks.

CASE 2.—L., aged 61, white, farmer's wife, had had no ground itch. The negroes on the plantation had it. The patient had had pains in the right side and uneasiness in the abdomen for the past six years, not related to meals; tenderness was not present. Physical examination showed nothing abnormal. There were a few eggs in the stools; no anemia. The patient recovered on treatment with thymol. Eight months later she was still well.

CASE 3.—Paul H., aged 42, male, white, lawyer, complained of indigestion and frequent headaches. He had tenderness in the right side of the abdomen. There were a few eggs in the stools. The patient was relieved of indigestion and headaches after the first course of thymol.

It would be impracticable to relate here enough cases to prove that the vague and indefinite symptoms referred to are frequently due to hookworms and that their occurrence in uncinariasis is not a coincidence. One who has met a large number of such cases and seen the prompt relief following treatment becomes convinced, I believe, that a very few worms may give rise to such symptoms without the production of anemia.

All who have had much experience with the disease have, however, seen cases with few worms and severe anemia. Hypersusceptibility to the toxin or possibly anaphylaxis may explain this. These cases form a striking contrast to what is seen in the negro with his many worms and no symptoms. Such instances should be regarded as cases of uncinariasis of medium or marked severity. They are often unrecognized through insufficient examination of feces. Many of the patients have had severer infection which has been reduced, but they have been unable to recover from the effects of the toxin. It is possible that old parasites may cease to ovulate long before they die. This hypothesis would explain cases in which there are few eggs and severe symptoms.

#### RECOGNITION OF THE OVA

The recognition of infections in which there are only a few parasites, or the determination of the moment when all parasites have disappeared under treatment, is not always easy. When many eggs are present, a positive report is easy to make; but when very few eggs are present it may require a long search over many slides before any can be found. To make a conscientious and reliable negative report, one must look over many slides if the ordinary technic is followed. I want to call attention to certain modifications of technic which make the examina-

tion far more reliable and save much time and labor. Following this technic one should find eggs if only one laying worm is present. This method of procedure is based on recognition of the specific gravity and shape of the eggs in relation to that of other material of the feces. Feces consist largely of bacteria, undigested food particles and crystals, insoluble grit, etc. The specific gravity of these different elements varies considerably. The specific gravity of fresh uncinaria eggs is between 1050 and 1100. When they grow old this is increased in many specimens.

A quantity of feces is well diluted with water, one in ten, and strained through gauze to get rid of coarse particles. This is centrifugalized, the fluid poured off, the centrifuge tube refilled and centrifugalized again until all the diluted feces have been used. The precipitate is rewashed several times with water as long as anything can be washed out. To know just how long to continue the centrifugalization is the secret of success. One must learn just what is the proper time for his centrifuge. It should be carried out at high speed and just long enough to throw the eggs to the bottom. Too long centrifugalization defeats the purpose. With a centrifuge running 3,500 revolutions per minute, ten seconds at first, when there is much matter, and then four to five seconds is usually the proper time. The centrifuge must be steady. This gets rid of most very small things, those having flat rough surfaces and those having a specific gravity about that of water. Now the precipitate should be washed as before, using calcium chlorid solution of a specific gravity up to 1050. (Calcium chlorid is preferable to other salts because of its hygroscopic property. This was suggested by Professor A. L. Metz.) This disposes of everything having a specific gravity below 1050, and the precipitate may now be examined. There frequently remains a considerable amount of material, much of which is considerably heavier than the eggs and of such a character that it interferes much with their recognition. This material may be removed by centrifugalizing with a solution sufficiently heavier than the eggs. A solution with a specific gravity of 1250 is very satisfactory. In such a solution the eggs go to the top and other material below. With an appropriate pipette one may remove a few drops from the surface and examine, or, what is still better, pour off some of the top fluid containing eggs, dilute with water sufficiently to bring the specific gravity below 1050 and centrifuge again. The precipitate will now contain most of the eggs contained in the original amount of feces and may all be put on one slide and examined. One such slide contains as many eggs as could be found in several hundred ordinary slide preparations of feces.

With this technic I was able to recover 96 per cent. of 1,000 eggs put in one ounce of feces, 94 per cent. of 100 eggs in the same quantity, and 60 per cent. of 10 eggs in one ounce. From specimens containing many eggs they may be obtained practically free from anything else. The accompanying illustrations show the results obtainable. I am indebted to Professor Beyer for making the photomicrographs from which the cuts were made.

The procedure may be of service when it is desired to obtain quantities of eggs free from feces for experimental purposes. It should be used before making a negative report or pronouncing a patient under treatment to be positively free from parasites. Good results can be obtained only with fresh specimens, and preferably those taken following a dose of epsom salts. In old specimens the specific gravity of the eggs may go even above 1250.

Before making use of this technic on questionable specimens the investigator should familiarize himself with just what is accomplished by the different steps, using specimens containing many eggs. Unless he does this and also tests his centrifuge he will be disappointed. Solutions of calcium chlorid of several different strengths should be used when it is desired to get eggs absolutely free from other material, but for ordinary diagnostic work two solutions, one of a specific gravity of 1050 and one of 1250, are sufficient. Washing with water alone is of much service.

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# CURRENT IDEAS ON APHASIA

## WITH STUDIES OF AN INTERESTING CASE\*

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STOCKTON, CAL.

### HISTORY OF THE THEORY OF APHASIA

The first observations on the subject of aphasia were made by Bouillaud in 1825 and by Dax, senior, in 1836, but the fundamental understanding of speech-defects and of their origin in lesions of the brain-cortex is due to the studies of Broca, who formulated the results of his researches in a declaration made before the Academy of Medicine of Paris in 1861, in which he claimed to have shown that the center of speech is located in the third frontal convolution of the left hemisphere. Since Broca, in the early seventies, finally succeeded in overcoming all opposition to his doctrine, establishing that the location of the speech center in the right hemisphere is found only in left-handed persons, the cerebral location of the center of speech has been moved more and more laterally and posteriorly in the cortex. It is especially to Wernicke's clinical and pathologic researches that we owe a fuller understanding of the subject. He has given us a scientific basis for the subdivision of aphasia into two distinct forms, a motor aphasia and a sensory aphasia, for the understanding of which it is necessary to assume the existence of three cortical centers, a motor center in Broca's convolution for the perception of speech-movements, a center for auditory word-pictures in the posterior half of the first temporal convolution, and a center for the visual word-pictures located more posteriorly in the angular gyrus. Wernicke and Déjerine do not recognize a special center for written word-pictures, but teach that efferent nerve-impulses pass from the visual and auditory centers directly to the general arm-center. Through these three centers each word-picture may be said to have three dimensions, an auditory, a visual and a motor-speech, each picture-dimension varying greatly in importance and in independence of the other two in different individuals.

Charcot divided man, in accordance with this idea, into three groups: *les auditifs*, in whom the sound-picture plays the greatest rôle;

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\*Paper read before the Sacramento Society for Medical Improvement, June 16, 1908.

*les visuels*, who depend largely on the optic pictures, and *les moteurs*, who make most use of the memory of spoken or written words.

The terms used in connection with the subject of aphasia have been manifold and many chaotic changes have been made in the application of the terms. Thus, Finkelburg applied the term "asymbolia" to aphasia in general. Aphasia was at one time confined to its motor form, while before that Broca (in 1865) suggested the term "aphemia" for motor aphasia. Now aphemia is applied by some to cases of pure word-deafness. Kussmaul's differentiation between amnesic and atactic aphasia is obsolete, because amnesia is present in all forms of aphasia.

Various terms are employed to define the elementary manifestations making up the defects of speech-functions. "Agraphia," a loss of ability to write, was first discovered as a symptom by Marcé in 1856 (the name "agraphia" was invented by W. Ogle in 1867). "Alexia" is the inability to read written or printed letters. "Amusia" is a loss of the ability to produce or comprehend music, and may accordingly be motor or sensory.<sup>1</sup> "Paraphasia" is an interchange of words. When the interchange is observed in reading or writing it becomes a "paralexia" or "paragraphia."

"Asymbolia," instead of being a term for aphasia in general, is now applied to a disturbance in the understanding of gestures (sensory asymbolia), or to a defective emission of motor impulses to produce gestures spontaneously or in reply (motor asymbolia). It is supposed to be caused by a focal lesion of the supramarginal gyrus and may or may not be combined with hemianopsia. Aphasia may sometimes, in the total absence of motor paralytic symptoms, be associated with an inability to handle or make use of objects in the manner for which they are designed. This perversion of muscular action has been termed "apraxia." An apractic patient may, for instance, put coins given him into his mouth, may not know what to do with matches or a match-box, may not know what to do with a knife, or he may not be able to close his eyes on command, or to open his mouth; he may use the spoon at the table very awkwardly, or, when told to take off his trousers, may help the left leg with his right hand, etc. The patient acts as if "his limb were absent-minded," and always shows the symptom, although he has understood the command fully. Apraxia may be observed in the right, but is usually present in the left extremity. It is only recently that this dis-

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1. A case of the latter form of amusia observed in the Stockton asylum in 1890-1892 was reported by me in the *Occidental Medical Times*, September, 1893. An excerpt was afterwards published in the *American Journal of Medical Sciences*, February, 1894.

turbance has been fully explained by H. Liepmann<sup>2</sup> of Berlin, who reported a case of motor apraxia in 1900. His findings have been corroborated by others. The disturbance is supposed to be due to lesions in the supramarginal gyrus and in the corpus callosum, where the lesion causes a destruction of the commissural fibers uniting one hemisphere with the other, making one hand—usually the left—guideless.

After Broca's doctrines of speech-localization had been undisputed for a period of half a century a neurologist came forward with a treatise in which he tried to establish proofs so completely upsetting this theory that his publication has acted—as Dr. August Wimmer<sup>3</sup> of Copenhagen puts it—like the battle signal of Roland's horn when it echoed through the valleys of Roncesvalles.

When the first article<sup>4</sup> of this noted neurologist, Prof. Pierre Marie of Paris, one of Charcot's most eminent pupils, appeared about two and a half years ago it could not fail to act like an earthquake to the current views on brain localization, as its title was, "Revision of the subject of aphasia: the left third frontal convolution plays no special rôle in the function of speech." While time will probably show that Marie has gone a step too far in making this positive statement, he is no doubt right in pointing out that the area of cortex destroyed is not a true index of the damage to the brain, the destruction subcortically extending in different directions and usually complicating the clinical picture by affecting the function of distant parts of the brain. In this way, he says, observers have fallen into error by ascribing all loss of function to lesion of the cortical area involved. Marie asserts that one finds cases of isolated destruction of the base of the left third frontal convolution in non-left-handed persons in whom there was no aphasia. He has observed one such case himself; and, on the other hand, says that he has met a case of pronounced Broca's aphasia without finding a lesion in this region of the brain. It is most singular that this part of Marie's personal study of the very brains which led Broca to make observations resulting in his epoch-making declaration in 1861 relative to the localization of the center of speech, a declaration which, though at first opposed by Trousseau, Vulpian and Charcot, was afterward established as a doctrine and almost became a dogma, helped along by the enthusiasm of his followers and the results of experiments of cortex-stimulation in the early seventies. Even Charcot finally adopted the teachings

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2. Liepmann (H.): Ueber die Rolle des Balkens beim Handeln, etc. *Allg. Ztschr. f. Psych.*, lxiv, 450.

3. Wimmer (August): *Hospital-tidende*, Oct. 23, 1907.

4. *Semaine méd.*, May 23, 1906.



of Broca. The brains above referred to are still found as specimens in the Musée Depuytren in Paris, and when they were examined by Marie it was found that Broca had examined them only on the surface and macroscopically. In the first of the two brains, Leborgne's case, Marie did find an affection of the left third frontal convolution, but he also found changes, and still greater ones, in the zone of Wernicke or zona lenticularis. In the second brain, Lelong's case, there were no pathologic changes in the last mentioned zone, but there was also an absence of characteristic lesions in the left third frontal gyrus. The brain was atrophic *in toto* and included an atrophy of the last mentioned gyrus, but what Broca considered a pathologic change is now looked on as a simple senile atrophy. The patient was eighty-four years old and probably presented symptoms of senile dementia.

A further declaration by Marie is that "every aphasic shows a more or less pronounced disturbance of the understanding of the spoken word, which defective understanding is less pronounced the more motor the type of aphasia." This disturbance in the word-understanding is not a word-deafness, as Wernicke says, but a loss of ability to understand the meaning of the concrete word—the aphasic of the motor type understanding a complicated command when repeated slowly a part at a time. Marie sees in this an enfeeblement of intelligence, which he considers a cardinal symptom of every aphasia, associated with loss of ability to read and write. Marie says that there is, therefore, but one cerebral location for aphasic disturbances, because there is but one aphasia. Broca's aphasia he considers an anarthria (due to a lesion in the lenticular nucleus, in the anterior knee of the internal capsule and in the capsula externa of the left as well as of the right hemisphere); that is, an incoordination—not a paralysis—of the muscles of speech, which incoordination is complicated with aphasia. Marie's one cerebral location for aphasia is Wernicke's zone (gyri supramarginalis et angularis), the base of the first<sup>5</sup> and second temporal convolutions.

Marie says that it is incorrect to speak of different centers as "word-center, visual-center or reading-center." Whenever Wernicke's zone is

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5. With regard to our present knowledge of the microscopic structure of the first temporal convolution, it may be here stated that Dr. Campbell, of Edinburgh, has demonstrated the presence of very large nerve-fibers and a certain cell-structure lamination in the posterior third of the first temporal convolution and the adjacent portion of the transverse gyri of Heschl within the Sylvian fissure, which join the posterior gyri of the insula. Campbell believes that this differentiates the above region sufficiently from the rest of the temporal lobe and the anterior part of the insula (which latter is probably olfactory in function) to be characterized as "the audito-sensory area."

affected we have the syndrome, Wernicke's aphasia, with the elements of word-deafness, alexia and agraphia, the degree of defect being proportional to the extent of the lesion. Broca's aphasia is, therefore, Wernicke's aphasia plus anarthria, which combination is so frequent, because it is due to softening caused by blood vessel disease, usually disease of the arteria fossæ Sylvii, which gives the vascular supply to certain parts of the cortex, principally bordering on the Sylvian fissure, as well as to certain parts of the central ganglia and neighboring white substance of the brain. The variations in the clinical pictures of aphasia are more dependent, according to Marie, on individual variations in the blood-vessel supply and anastomoses than on the topography of the cerebral convolutions affected.

While some of Marie's conclusions are true, or at least worthy of serious consideration, others have provoked sharp contradictions, both in France and Germany. In France it is Déjerine especially who has criticised them. In a masterly manner Déjerine points out that, even if the speech-understanding is at times—though not necessarily—affected in motor aphasia, it is much less so than in the sensory form, and, when found in the patient directly after the insult, it disappears quickly with the initial alexia and agraphia. Déjerine also insists that a pronounced and permanent anarthria can not be caused by a lesion in the lenticular nucleus, and he states that he has never seen a pronounced anarthria following a unilateral lesion, whether in the cortex or in the internal capsule. The great majority of writers make a sharp distinction between anarthria and motor aphasia. The few words still at the command of the motor aphasic are well articulated, and, as Déjerine says, one may meet patients suffering from this form who can sing melodies learned prior to their illness with absolute correctness, both as to pitch and time, while it is impossible for them to cite the words; "the patient with motor aphasia is, therefore, not suffering from dysarthria." "The aphasic can pronounce only a few words—the sufferer from anarthria all words, but badly." On the subject of intelligence-defects in the aphasic Déjerine has pointed out that a general paralytic can speak and write, and his feeble-mindedness is much more pronounced than the intelligence-defects observed in an aphasic individual.

In Germany Heilbronner, Liepmann, Henneberg and others have expressed the same views as Déjerine. The first-mentioned believes that the intelligence-defects observed by Marie are in a large measure the result of misinterpretation of the symptom of apraxia.

When Marie's teachings were discussed at a meeting of the *Société de neurologie de Paris* (Nov. 8, 1906) Dr. André Thomas said that he

did not deny that in some cases of aphasia there might be a diminution of intelligence, but he attributed it to a more or less marked disturbance of the "inner speech." This "inner speech" is the mental repetition of words or sentences subconsciously practiced in understanding the spoken word. In motor aphasia there is an interruption in the transfer of the word-picture (that is, the sound-picture) to the motor speech-apparatus, which makes the memorizing difficult, to which becomes added a further difficulty in the reproduction itself of the word-picture. Marie's doctrine of loss of intelligence in the aphasic has been considered the least tenable of his new theories.

In spite of the large clinical material which is at the command of Déjerine, he has so far been able to furnish but two cases to prove that Broca's aphasia may be caused by an isolated destruction of the third frontal gyrus, and these were published about a year and a half ago (May, 1907). The two cases published by Déjerine some months before this to illustrate motor aphasia did not stand the scrutiny of Marie, who in a later article showed that the lesion extended in one of the cases beyond Broca's region into the white substance under the gyrus supra-marginalis or the neighborhood of the zone of Wernicke, while in the other case Marie shows that, besides the cortical lesion, a degeneration was found in the internal capsule and the external part of the thalamus. In justice to Marie it must be admitted that it is surprising that the medical literature has so far furnished so few clear cases in proof of the existence of Broca's center. The justification for its elimination, however, has not been fully established.

#### REPORT OF CASE

During the past year I have studied a very interesting case of aphasia at the Stockton State Hospital. It was interesting because of the complete word-deafness present, especially in the early part of the history of the case, combined with complete alexia and agraphia and a certain degree of apraxia mixed with asymbolia, the patient appearing at the same time to be quite intelligent considering his age and the symptom-complexes present. He was neat in person, energetic in his attempts to make the nurses understand his wants and attentive to his fellow patients. He showed acuteness in visual apperception and his behavior as to affects seemed quite normal. Besides being clinically interesting, the pathologic findings have a certain bearing on the questions stirred up by Marie's publications. The encephalomalacia found in the case was

without doubt caused by the lodging of an embolus in the artery of the left Sylvian fissure. In such cases it is, of course, extremely difficult to decide how far the symptoms present during life were due to destruction of gray matter of a certain locality or to degeneration in the underlying white matter, which contains not only afferent and efferent neurons, but also association-fibers connecting more distant parts of the cortex.

*History.*—J. G. W., aged 72, farmer, well nourished for his age, was admitted to the institution June 26, 1907. From relatives it was learned that there was no history of insanity or nervous diseases in the family, but his father and sisters were said to have been subject to attacks of articular rheumatism and heart trouble. There was no history of apoplexy. He had enjoyed very good health all his life until about twelve years before admission, when disturbances referable to the heart began to set in; these, however, were slight, consisting of palpitation, some sensation in the region of the heart and dyspnea on exertion. Prior to May 6, 1907, he did light work about the house, was active for his age, interested in the newspapers and wrote a good average hand. He had always been right-handed.

*Present Illness.*—On the morning of May 6, while he was dressing himself, his wife, who was in an adjoining room, heard him fall, and on going to him found him lying in an unconscious state on the floor. He could not be aroused and remained in this condition about three days, when he gradually recovered consciousness and could say two or three words. The attending physician reported that he was quite prostrated, apparently equally helpless in all four extremities. No paralysis in the face was observable, but a speech-difficulty was apparent. He could say only a few words, which were misapplied, could not make himself understood, nor could he understand what was said to him. No detailed investigation into the nature of the manifestations was made at this time. About a month after the attack began he was able to leave his bed and seemed to have about equal strength in the right and left extremities, but showed the same difficulty in understanding and making himself understood, and seemed confused and irritable because the family could not carry out his wishes. This irritability kept on increasing until about a week before his commitment, when he became threatening and violent, frightening his family and the neighbors so that they finally had him sent to the asylum.

*Examination.*—When he arrived at the institution the patient seemed to have become quiet and showed no excitement or irritability. He seemed well preserved for his age as far as his outward appearance was concerned. His pulse was 70, irregular and intermittent every five to seven beats, radials and temporals arteriosclerotic. Heart dulness extended to the upper border of the third rib and to the right border of sternum; apex beat was in the mammillary line. A faint systolic murmur was heard at the ensiform and at apex; the diastolic tone was roughened. Pulsation of the carotids was visible in the neck. Lower border of the liver was sensitive to pressure, and found about one inch above umbilicus. The spleen was not perceptibly enlarged. Auscultation of the lungs showed nothing pathologic. The cranium was fairly symmetrical, not sensitive to percussion. There was no edematous swelling of face, and no defective function of eye muscles. Pupils reacted normally and equality was present. Fundus: Right eye showed optic disk of normal color with clear-cut margins and without cupping. The blood vessels showed distinct pulsation in the veins. Left eye: Chorioidal

atrophy around rim of disk, which was otherwise normal. Pulsation of veins likewise observed—not of arteries. Perimetric examination of the field of vision gave the results shown in Figure 1.

There was slight inequality in the right side of the face: the upper nerve branches not involved. The tongue pointed straight and was equally movable; soft palate normally suspended; sensibility in face normal. The patient had good use of his upper extremities. The dynamometer showed  $42\frac{1}{2}$  in the right, 59 in the left hand. There was no muscular atrophy; sensibility and reflexes normal. The patient's walk was erect, gait normal, muscular strength in lower extremities about equal. There was no incoordination in upper or lower extremities. Romberg was present to a slight extent. There was no atrophy of muscles in lower extremities. The knee-jerks were equal and about normal; other tendon-reflexes and skin-reflexes likewise. The bowels were fairly regular; no symptoms of indigestion. Urine contained no albumin or sugar. The patient made the impression of being quite bright and active. He was fairly well oriented as to time and place; his behavior was orderly, the state of affects was quiet and the attention was markedly present. There were no symptoms of confusion and no hallucinations or delusions ascertainable. He was cleanly in habits.

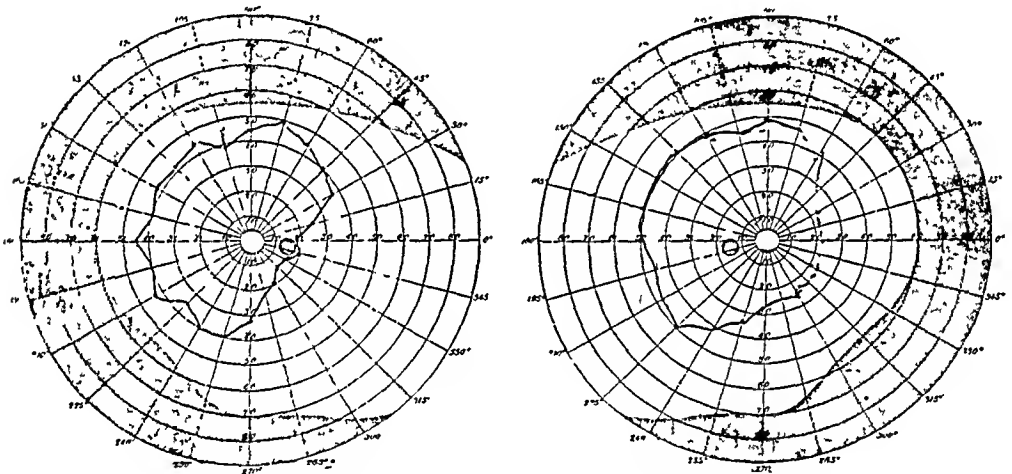


Fig. 1.—Perimetric examination of patient's field of vision.

1. *Examination of the Speech-Ability.*—In talking with the patient it is at once noticeable that he used only a few words, but these words are well pronounced—the stamp is nearly perfect, no trace of inarticulation.

A.—*Spontaneous Speech:* This is characterized by a search for words and by paraphasia. Being paraphasic his words are, of course, usually irrelevant and sometimes unintelligible but not muffled.

B.—*Repetition of Words Spoken by Examiner:* Short simple words in common use he repeats fairly well, as “good morning.” Uncommon or longer words he can not repeat.

Examiner, requesting patient to repeat: “This is the 16th of September.”

Patient: “This is— Say, I don't know as I understand that name just exactly.”

Examiner: “This is the 16th of September.”

Patient: “I don't understand it.”

Examiner: “To-day is Thursday.”

Patient: “Yes, sir.”

Examiner: “You repeat, this is 1907.”

Patient: "This is 19— site, site, he it. I can't do it."

Examiner: "They have commenced to pave the streets."

Patient: "They went to work, to see him at the work."

C.—Understanding of Speech: The patient now and then fails to understand the words spoken to him, sometimes not when the question has been repeated several times; and when he replies to questions he tries to employ circumlocutions and uses paraphasic expressions. At first he answers questions in a quiet way but soon shows excitement and paraphasic expressions are uttered more and more until a jargon is the result, or, as the Germans say, *Wortsalat*. He is visibly annoyed by his failures and makes earnest efforts to overcome them; sometimes he succeeds and shows he is conscious of his inefficiency.

Examiner: "What is your name?"

Patient: "It's G. G. G. J. Hoppa in Wallapalla."

Examiner: "How old are you?"

Patient: "152 reason—yes s'n, I have; sometimes I can step as well as can be, sometimes I can't do it."

Examiner: "Where were you born?"

Patient: "The doctor, doctor, you want me allow where I do; don't you? Derwood. It was Annie Lary—he lives in assent, absert, all on postaros; some of them was of the colatos. You could say it, but I can't say it sometimes. Sometimes for two or three days, I will just see it all right."

Examiner: "Where are your people?"

Patient: "She has the ageration of pusen of noderats of all the people, and I want to say enough to now my father—the last she says and he lived with her, my father. You don't want to see she is out of the opponies of one all elderly of this country so winisin, nor nothing of the kind. I never tried to hurt any one; well sir I can't tell you in a minute, if I can think of it, if I can see it, all right."

Examiner: "How eame you to be here?"

Patient: "No, sir. I never tried to hurt anybody in my life, the brother: no sir, I never did, and they done it, that is more; just as quick as I can used among the lose. Never in my life have I been in an asylum. No sir, I never had the thoughtness. I was so hurt with it."

D.—Identification of Objects: The patient hardly ever names the object correctly, or identifies it from among a number of names, although he sometimes recollects part of the word or something resembling it; frequently he circumlocutes.

Examiner: Shows patient a key.

Patient: "No sir, it is no medicine, it majiness."

Examiner shows an ink-bottle.

Patient: "Quickness. I guess, doctor. I should think it was."

Examiner shows seissors.

Patient: "It will cut the rappa, you can get of that cotta."

Examiner shows a postage stamp and asks: "Is that a pen-knife, a pencil or a stamp?"

Patient: "Well, sir, it was a hipna of the masons, the ridamite of the doctor."

Examiner shows a pair of seissors again.

Patient: "Seisson, sitton, chisel, shudden, seissum, sieum, hipple: an aggitator of this shittum that cut it up and sent them all up together for a long with somebody else."

Three pieces of paper of different length being placed on the table, the patient is asked to give to the doctor the longest.

He takes hold of the longest but leaves it on the table.

Examiner: "Give me the smallest of the three pieces."

He picks out the correct piece but leaves it on the table when told to give it to the doctor.

Examiner: "Pick out the medium-sized paper and give it to me."

Patient (He doesn't seem to understand): "I can't say that I did; that light person there—that doctor there (pointing to the nurse) can tell you just as much about it as I can. You want the bigginess pound?" Picks out the largest piece of paper.

He is told to rise, go to the bed and get the paper and put it on the table. He does so correctly.

When told to get up from his chair, shut the door and go and get the smallest piece of paper and give it to the nurse, he rises from his chair, goes past the door into the hall and asks: "Did you want me to go out?"

When told again to do the same thing, the command being repeated three times, he gets up from his chair, goes out into the hall and says: "I will come when you are ready."

2. *Ability to Read.*—The patient was given his spectacles and told to read aloud the word "Monterey."

Patient: "Yes, sir, he is appola, mesia, anesia, meni, memisia, deme."

Pointing to one letter at a time of the word "Monterey," the examiner asks the patient to name each letter.

M—"Doctor."

O—"Munet."

N—"Nego."

T—"GO."

E—"Eda."

R—"Derider."

E—"Hita."

Y—"Juney."

When asked to read "Joseph," spelling it, he spells, "M, w, j, h."

Asked to read the word "hat," he reads, "Sateh," "book," "kemipy."

Asked to spell "Stoekton," he spells, "S, g, j, g, n, e, j, g."

He had just before been asked to read "J. G. Wright," which he did correctly. These are the only letters and word he recognizes.

In cases of motor aphasia in which alexia did not seem to be present, it was found by Déjerine (1895) that latent disturbances in the ability to read are often discovered. These are ascertained through the fact that, although the patient is able to read words written or printed in the usual manner, he can not read them when the letters are written a certain distance apart or when written in a vertical line instead of horizontally. Although our patient can read his name as above, he fails when subjected to Déjerine's test. He is not only unable to read aloud, but when asked to read to himself and requested to tell what he has read it is found that he has not understood a word. He was given a letter from his wife to read, which he read fluently and with the utmost confidence, only now and then hesitating a little when looking at certain words, continuing with a significant nod of the head, as if to express satisfaction with his interpretation. He read in part as follows: "I heard them, we believe them, in life. I think that I heard them—that I believed them—that I heard them. I think that I lived them in the. . . when we heard them. I thought them that if when we heard them I lived in belief—I heard them. I did not then, that it each had that they both of them in the wife in them when I live when we both them in the help we had," etc. When asked to give the number of syllables in a given word by gesture (putting up fingers), after careful explanation of what is expected of him, he fails. For instance: Broom—two, wagon—two, pen—one, floor—two, bedstead—two, sunlight—one, etc. This defect of the inner speech is in this case

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shown to be present in cortical sensory aphasia, which Sahli in his last edition says has not yet been met with.

3. *Ability to Write*.—A. Spontaneous writing: This frequently amounts to an illegible scrawl—resembling that of a child of two or three. In the writing one can recognize "w," "j" and "G," and one or two other letters here and there, as illustrated in the appended letter to his wife.

*I G Wright*

*I finger*

*Don't forget me.  
I love you  
I am very glad to  
see you  
and can  
see you and see*

*can see the one  
in the house.*

B. Writing from dictation: The examiner, showing the patient a hat and making him repeat the word "hat," says: "Now, write down the word 'hat.'" The patient writes:

*CD 22*

Examiner (pointing to and taking hold of the patient's right hand): "What do you call this, Mr. Wright?"  
Patient: "That is Wright—no, my right hand."  
Examiner: "Now repeat the word 'hand.'" Patient: "Yes."  
Examiner: "No, you say 'hand.'" Patient: "Yes, I do."  
Examiner: "No, say 'hand.'" Patient: "Hand."  
Examiner: "Now, you write 'hand.'" Patient: "Hand."



Patient writes:

*stove*

Examiner: "Now, write down at my dictation the word 'stove.' I will spell it, and you write one letter at a time. S t o v e."

Patient writes:

*J B ite as e*

Examiner: "Now, write at my dictation your first name, 'Joseph.' I will spell it, giving you one letter at a time before you write: J o s e p h."

Patient writes:

*J. a J - r n J p e n*

A letter to his wife, consisting of the simplest words in three or four lines and running as follows, is dictated to him:

Dear Wife:—I received your letter yesterday and was glad to hear from you. Yours truly.

The patient writes:

*Dear*  
*My dear*  
*I received your letter*  
*and was glad to hear from you*  
*Yours truly*  
*J. W. Henry*

That he understood the dictation, in a general way at least, is shown by the scribbling for "dear wife" and "yours truly," being short lines. Below the "yours truly" appears in proper place what is meant for his signature, which is sometimes written so that it can be read; at other times only part of it is legible.

Told to write his name, the patient writes as follows:

*J. W. Henry*

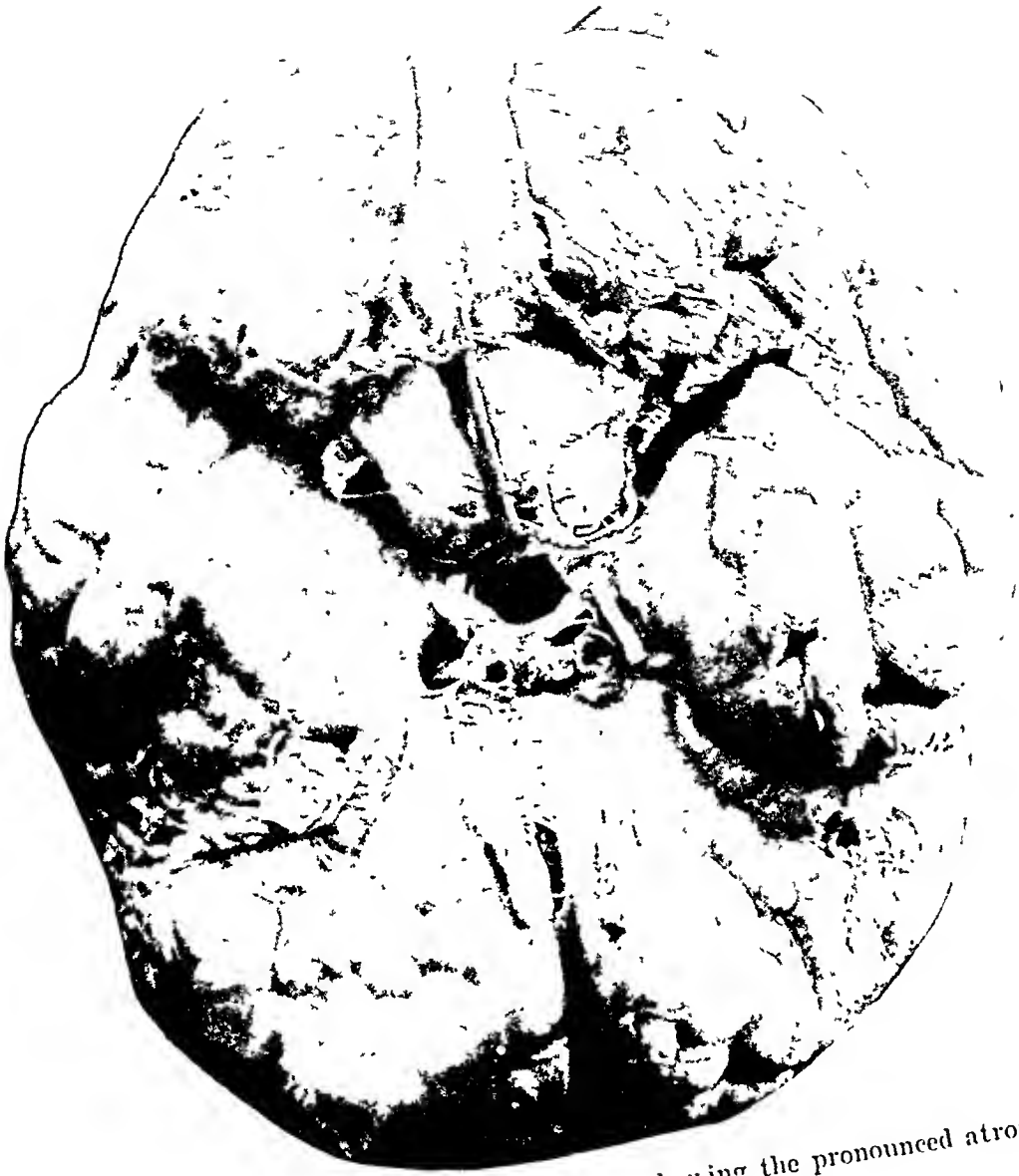


Fig. 2.—View of the base of the brain, showing the pronounced atrophy of the anterior portion of the left temporal lobe.

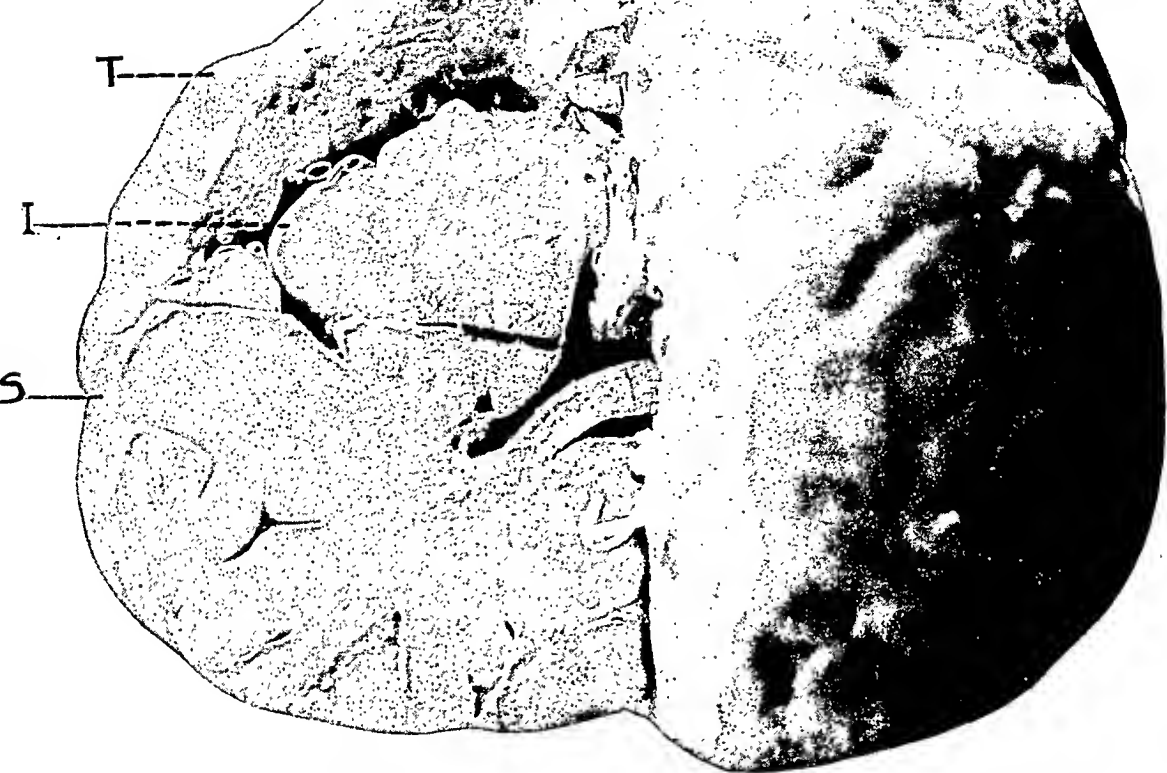


Fig. 3.—View of the anterior sectional surface of the frontal section of the left hemisphere, showing the atrophy of the temporal lobe, which increases from the basal surface toward the fissure of Sylvius; T., temporal lobe; I, insula or isle of Reil; F. S., fissure of Sylvius.

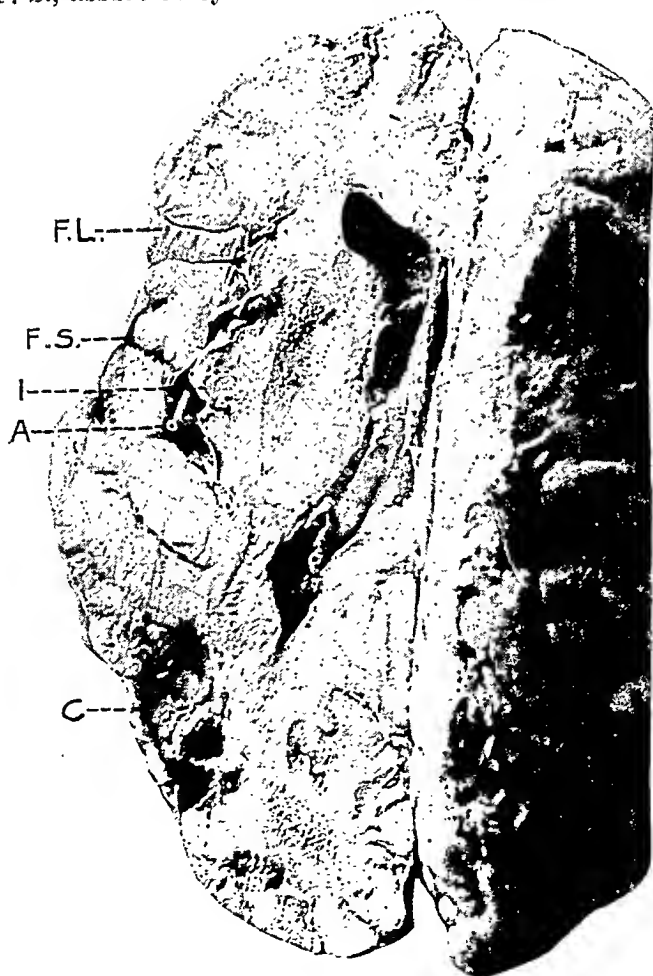


Fig. 4.—Basal sectional surface of the horizontal section of the left hemisphere, showing location of the large cavity with malaciac surroundings in the posterior part of the brain; F. L., frontal lobe; F. S., Sylvian fissure; I., insula; A, anterior; C, posterior.

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Told to write "Lodi," he writes:


22-

Told to write "Lodi," he writes

To the dictation of the isolated letters shown below, he writes the characters


appended:

**A:**



D: ~~2/3~~

**H:**

J: 

G: *Sh*

**L:** *[Handwritten signature]*

ME: *2*

0.

W: 5

S: us

He has always been right-handed and writes better with his right hand. The scribbling with the left hand shows no evidence of mirror-writing, which has often been observed in agraphia of left-handed persons. Told to write the figure 3, he writes a W; told to write the figure 4, he writes a W. He can not write numbers from dictation and can not read them, but can write them spontaneously to a very limited extent in series, but he can not write beyond 9. He frequently skips numbers or repeats them and inserts now and then J and W. Asked, "What is your age?" he replies: "I am 72 years old." Told to write "72," he writes the three initials of his name, "G. J. W." This symptom, called perseveration, is frequently observed in aphasia, alexia, agraphia and disturbances of the gesture-speech, and consists of a sticking to a certain innervation (Haftenbleiben). This was especially illustrated when studying series. Told to say the alphabet, he says: "A, b, c, d, e, f, g, h, J. G. Wright," laughs and says: "J. G. W., J. G. G.," repeating this three times, until he gives it up in disgust. When counting, "1, 2, 3, 4," etc., and the physician whispers "J. G.," he inserts these and is unable to proceed; begins again with "1, 2, 3," etc., and the same phenomenon repeats itself.

Copying: The patient is unable to copy letters and only to a slight extent succeeds in copying squares and triangles, but very imperfectly. Illustrated in the following two or three lines given to him as dictation:

C.—Copying: The patient is unable to copy letters and only to a slight extent figures. He succeeds in copying squares and triangles, but very imperfectly. His writing from copy is illustrated in the following two or three lines of the same letter to his wife which, as told above, was given to him as dictation:

Charles  
 and all  
 to you  
 I am  
 your  
 John P.

4. Musical Perception.—The patient had received no musical training but he had been able to sing a little and to whistle. Examination as to his expressive musical ability showed this to be fairly intact under the circumstances.

as he was able to continue songs like "The Star-Spangled Banner" and "Yankee Doodle," when the first five or six notes had been sung or whistled by the examiner.

5. *Test of Gestures*.—A. Spontaneous gestures: The patient makes use of spontaneous gestures fairly well; nods his head and moves his hand in greeting, points to objects and makes use of other gestures fairly well when trying to make himself understood.

B.—Gestures by Dictation: The patient responds to commands faultily, which is no doubt partly due to his failure to understand the commands.

C.—Imitation of Gestures: It is especially noticed that the patient imitates poorly with his left hand.

The patient's right hand being held by a nurse, the physician asks him to imitate with his left hand:

Physician touches point of nose with left index finger.

Patient puts flat hand to the side of his face.

Physician repeats this gesture.

Patient puts flat hand to side of head.

Physician puts two fingers parallel across his eyebrow.

Patient covers his whole face with his hand.

Physician puts one finger over the closed eyelid.

Patient again covers the whole face with his hand.

Physician puts index finger in his mouth.

Patient puts four fingers into his mouth.

Physician makes military salute.

Patient covers his mouth with his hand.

6.—*Understanding of the Use of Objects*.—As a rule, the patient seems to understand how to use a variety of utensils and other objects. Occasionally there is a trace of apraxia present.

Shown a spoon, he is asked, "How do you use that?"

He replies: "Bad medicine—yes, it might be something of the kind—or strong medicine"; then uses it correctly.

Shown a matchbox, he is asked what it is.

"It's pump. I think it is a machine for clocking—to burn anything."

He is asked to use it.

He opens the box, takes out a match and tries to strike it on the top of the box (wears spectacles at the time). After a couple of futile attempts he uses the side of the box.

Given a pencil, he uses it upside down.

On a subsequent day he put on his shoe and took it off properly, closed a knife and used a corkscrew and other objects correctly. He can not make the simplest arithmetical computation orally, no doubt in part because he doesn't understand: For instance:

$2 \times 2 = 12$ ;  $5 \times 6 = 72$ ;  $3 \times 3 = 15$ ;  $6 \times 6 = 72$ .  $\$2 - \$1 = \$6$ .

This is out of keeping with his intelligence in other respects. Asked to put on his spectacles, he replies: "I have them here," putting his hand in his left side coat pocket at once and finding them. He had not made use of them that morning. He missed a fellow patient who had made his escape, etc.

#### SUMMARY OF RESULTS OF EXAMINATION

Summing up the findings in the case, we have in the above a cortical sensory aphasia, which is associated with a trace of apraxia and with asymbolia. There is present a loss of understanding of spoken language and inability to repeat words. The speech is paraphasic. Spontaneous and dictated writing are lost; likewise understanding of language written by the patient and reading aloud as

well as understanding of what has been read. Copying is present but defective. These defects are not complete in all the spheres; the lesion has left certain remnants of association-fibers intact. The symptom-complex is therefore made up of aphasia, alexia, agraphia, to a slight extent apraxia and asymbolia. It is possible that the lesion, which probably was caused by an embolism resulting in cerebral malacia, is multiple, one being located in the sensory speech-center of Wernicke in the first temporal convolution, the other in the angular gyrus. The presence of asymbolia, contracted fields of vision which amount to an incomplete right-sided homonymous hemianopsia, and the partial loss of ability to copy, speak for this second lesion extending in to the occipital lobe.

#### PATIENT'S LATER HISTORY

After this clinical report had been read at the meeting of the San Joaquin Valley Medical Association, which met at Fresno, Nov. 13, 1907, the patient's condition remained about the same as far as the aphasic symptom-complex was concerned until the following March. He had been subject to attacks of bronchitis with asthma for years, and a severe attack of this kind set in about March 10, which was followed by a capillary bronchitis to which he succumbed on March 21, 1908.

#### AUTOPSY

An autopsy was permitted on the brain only and was performed eight hours after death. The walls of the cranium were found below the average in thickness; there were marked adhesions along the sagittal suture. The dura mater seemed normal in appearance, and on incision allowed a moderate amount of cerebrospinal fluid to escape. The pia-arachnoid was found milky and thickened over the convexity of the hemispheres, especially over the left, which posterior to the frontal lobes showed a flattening of the surface, most marked behind the Sylvian fissure in the temporal lobe, the contours of this lobe being in marked contrast with those of the corresponding lobe of the right hemisphere, as shown in Figure 2. The greater part of the left temporal lobe had a gelatinous appearance, and when the brain was handled showed a fluctuating movement of its surface. The cerebral arteries presented marked arteriosclerotic changes, especially the anterior cerebral and *arteria fossæ Sylvii*. The flattened or atrophied portion of the temporal lobe extended from the beginning of the first temporal gyrus in the Sylvian fissure nearly to its center, took in the anterior one-third of the second temporal and a small portion of the anterior one-third of the third temporal gyrus, a small hemorrhagic cyst being found in the last-mentioned locality. Corresponding to the convolution surrounding the lower of the two terminal branches of *ramus horizontalis post* of the Sylvian fissure was another small cyst, and a third hemorrhagic cyst, lenticular in form and of the size of a large bean, was found on the area surrounding the posterior termination of the first temporal fissure and laterally from the interparietal fissure, that is, in about the location of the gyrus angularis. A horizontal cut was made through the left hemisphere about on a level with the center of the genu of corpus callosum in front and the posterior projection of the thalamus opticus behind. This section crossed the Sylvian fissure about the center of the operculum, passed about 0.6 cm. below the inferior limits of the small cyst—afterward located in the neighborhood of the supramarginal region and passed through the elongated cyst in the lower part of the angular gyrus. A frontal section was made about perpendicularly to this, and about along line 4—4 of Hermann's Plano-projection.<sup>6</sup> The cut passed through the anterior part of the operculum and the atrophied portion of the anterior part of the temporal lobe. The anterior sectional surface of this cut is seen in Figure 3, which shows the outlines of the section of the temporal

6. Fig. 25, von Monakow's *Gehirnpathologie*, p. 37.

lobe in this locality to taper from a fairly broad base in its inferior portion to almost a point where it terminates in the horizontal cut. In its upper part the cortex is entirely absent. Additional sections into the frontal convolutions revealed no microscopic pathologic changes. The surface of the horizontal section is shown in Figure 4. In the posterior parts of these was found a large destruction of brain tissue. An elongated cavity lined with a brownish-colored detritus extended below the cortex, or in part of its extent just beneath the pia for a distance of about 3.8 cm., completely undermining and, in fact, in most of its extent, destroying the cortex in the region of the gyrus angularis and the convolutions anterior to it. The cavity measured about 1.9 cm. in depth, that is, in the direction of the medullary substance, and its deepest part was below the cyst which was visible on the convolutional surface. A small irregularly shaped malacial change, about 0.4 cm. in diameter, was found below the cortex of the second occipital lobe. The outlines of the cavities are plainly visible in the illustrations. A section made through the center of the supramarginal gyrus showed no pathologic changes, but when another perpendicular section was made in the convolution just in front of this gyrus a malacial cavity was exposed, measuring 0.6 cm. by 0.75 cm. The largest cyst extended anteriorly in the direction of the cyst found in front and beneath the supramarginal gyrus. In other words, the malacial changes described were found in the left temporal lobe involving the location of the gyrus lenticularis of Wernicke, extending from here into the region of the angular gyrus and the second occipital convolution.

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# THE DIAGNOSTIC VALUE OF HEMOLYSIS IN CASES OF CANCER

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Recent researches on various biologic properties of the blood in cases of cancer have given hope that a diagnostic blood test could be found. Of these studies none at first seemed more promising than those which dealt with the hemolytic properties of the blood serum.

Within the last year the statements of Crile have aroused much expectation. Crile found the occurrence of isohemolytic serum so very frequent (80 to 100 per cent. of the cases) in carcinoma, and so very rare in other diseases, that from his work there seemed little doubt that the hemolytic reaction would be exceedingly valuable in diagnosis. Other workers, however, have not confirmed his findings, and the whole question as to the value of this method required re-examination.

With the aid of a modified technic, the chief advantage of which is that it enables us to perform a large number of tests readily with a small amount of blood, we examined 100 persons.<sup>1</sup> These were taken in groups of ten or fifteen, the serum of each one of the groups being tried in turn on the washed red blood cells of every other member of the group. The usual controls of each variety of red cells with its own serum and with salt solution were made.

The question of technic, which will only be touched on briefly here, is of considerable importance in comparing the results of different workers. In a preliminary series of 100 cases (over 1,500 individual tests) we attempted to settle for ourselves various questions of technic. We believe that the method which we have finally adopted (and which is described above) gives results strictly comparable with those of the usual method. It may be admitted, as a theoretical possibility, that an exceedingly faint trace of hemolysis might be overlooked in this method, on account of the smaller diameter of the tubes (3.5 to 4 millimeters as compared with the usual 8 to 10 millimeter test-tubes). In practice this source of error is negligible.<sup>2</sup> The method of preparing the erythro-

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1. The majority of these cases were in Mt. Sinai Hospital. The blood of some was kindly supplied us by Dr. R. Weil from the German Hospital, and by Dr. Brewer and Dr. James from patients in Roosevelt Hospital.

2. In these tests, at the suggestion of Dr. Weil, the serum was used in concentrated form—3 parts of serum to 1 of 20 per cent. red-cell suspension, so that the cells were present in 5 per cent. strength in the mixture.



cyte suspension used by Crile, which has not been published, but which Dr. Crile was kind enough to communicate to us by letter, was given up, after having been tried in sixty-nine cases, because of the inconstant results.

The nature of the results can best be appreciated by reference to the accompanying tables. The intensity of the hemolysis in each test is indicated approximately by the number of plus marks. The horizontal columns represent sera, the vertical columns the corresponding blood cells. It will be noticed that even strongly hemolytic sera seldom lysis more than half of the different varieties of red blood cells with which they are mixed. In doing the experiments, it should be said, the tubes were numbered by another person in such a way that the person who made the readings was not aware which blood he was examining.

The results, as a whole, without regard to the intensity of the reaction or the number of different kinds of red cells hemolysed by each serum, may be summarized as follows:

Of the 100 subjects 38 were suffering from malignant tumors, 40 had other diseases and 22 were apparently healthy. (The diagnosis in nearly all of the tumor cases was confirmed by operation and microscopic report. The diagnosis in the other cases rested generally on clinical data.)

In the 38 cases of malignant tumor, 28 patients had serum which was hemolytic—a proportion of 76 per cent. In the 40 other diseases, 20 patients had hemolytic sera (50 per cent.). Of these, 6 were cases of tuberculosis—a well-recognized cause of isohemolysis; 5 of the 6 sera were hemolytic. If we exclude the tuberculous cases, 15 cases, that is 42 per cent., of the 35 remaining cases of disease were hemolytic. The diagnoses in these cases were as follows:

- Cases 151 and 75.—Fibroadenoma of breast (two cases).
- Case 95.—Catarrhal jaundice.
- Case 94.—Chronic gastritis (?).
- Case 108.—Postpartum general infection.
- Case 124.—Postoperative adhesions (gall bladder).
- Case 138.—Diffuse lipoma.
- Case 147.—Subacute bacterial endocarditis and streptococemia.
- Case 162.—Diabetes mellitus.
- Case 164.—Endocarditis (chronic).
- Case 169.—Appendicitis.
- Case 178.—Colloid goiter.
- Case 180.—Plumbism.
- Case 185.—Hodgkin's disease.
- Case 127.—Chronic thyroiditis (tuberculous).

Of the 22 normal persons, 1 showed hemolysis (5 per cent.) This was a patient who had been operated on for hernia several weeks before and in whom no signs or symptoms of any disease could be elicited.

TABLE 1.—HEMOLYSIS IN CANCER PATIENTS AND OTHER SUBJECTS

Subjects .....	Red Blood Cells.									
	131	133	134	135	136	137	138	140	141	142
Normal .....	—	—	—	—	—	—	—	—	—	—
Fibroadenoma breast..	++	—	++++	++++	—	—	—	+	—	++++
Carcinoma liver .....	—	—	—	—	—	—	—	—	—	—
Tuberculosis .....	—	—	—	—	—	—	—	—	—	—
Tuberculosis .....	+	+	—	—	—	—	—	+	—	+
Tuberculosis .....	—	+	+	++	—	—	—	++	—	++
Normal (hernia) .....	++	+++	++++	++	—	—	—	++	—	++
Lipoma .....	+	++	++	++	—	—	—	+	—	—
Epithelioma jaw .....	+	—	++	++	+	—	—	—	—	—
Carcinoma rectum ....	—	—	—	—	—	—	—	—	—	—
Normal .....	—	—	—	—	—	—	—	—	—	—
Carcinoma .....	—	—	—	—	+	—	—	—	—	—
Rodent ulcer .....	—	—	—	—	—	—	—	—	—	—
Rodent ulcer .....	++	+	—	—	—	—	—	—	—	—
Normal .....	—	—	—	—	—	—	—	—	—	—
Normal .....	—	—	—	—	—	—	—	—	—	—
Control .....	—	—	—	—	—	—	—	—	—	—

Serum

If we attempt to make the work to some extent quantitative by having regard only to the pronounced hemolyses (indicated by two or more vertical marks in the tables), the percentage of positive results in malignant disease as compared with other diseases is somewhat better. Nineteen of the 27 sera which gave strong hemolysis were from cases of cancer (74 per cent.). That is, 50 per cent. of the 38 cases of cancer gave strong hemolysis. Seven cases (17 per cent.) of the 40 other diseases examined also gave very pronounced hemolyses and the 1 hemolytic case in the group of normals also showed a very strong hemolysis. These actively lytic cases were as follows: Case 94, chronic gastritis (?); Case 127, chronic thyroiditis (tuberculous); Case 137, normal (hernia); Case 138, diffuse lipoma; Case 178, colloid goiter; Case 180, lead-poisoning; Case 181, tuberculosis; Case 75, fibroadenoma of breast. These results are curiously parallel with those obtained by Kelling's method, in which the lytic effect of human sera on chicken red cells is estimated quantitatively and only the strong hemolyses are regarded as positive. (His interesting experiments require confirmation.)

Other methods of analysis give results less favorable (as far as diagnostic possibilities are concerned) than this. Thus taking the mere number of different varieties of red cells out of all those subjected to each serum, and setting up three as an arbitrary standard, we find that of the 42 sera which laked three or more different varieties of red cells, 24 were from cases of malignancy, whereas of the 16 sera which laked only one or two varieties of cells, 10 were from cases of cancer.

Likewise with the method introduced by Weil, "based not only on the reaction of the serum, but also on the degree of resistance of the corpuscles to that serum," it is seen that generally a given hemolytic serum falls into Weil's first group (hemolytic toward non-cancer corpuscles, but not toward cancer corpuscles), or his second group (lytic to both kinds of corpuscles), chiefly according to whether it is a weakly or strongly lytic serum. Of 25 cases belonging to the first group, 14 were cases of malignant tumor; of 29 belonging to the second group, 17 were cancer cases; the grouping therefore seems to have no special significance.

If attention is paid only to the resistance of the red blood cells (and the high resistance of cancer red blood cells to all sorts of lytic agents has been recognized for years), it is seen that red blood cells resistant to all the sera applied to them occurred chiefly in those cases whose serum was itself hemolytic, and not much more frequently in cancer than in

TABLE 2.—HEMOLYSIS IN CANCER PATIENTS AND OTHER SUBJECTS

Subjects .....	Red Blood Cells.*														
	157	154	152	156	148	150	147	155	158	151	153	149	142	140	
Carcinoma of stomach.....	157	—	—	—	++	—	+++	++	—	+	+	—	—	++	
Normal .....	154	+	—	—	—	++	—	—	—	—	—	—	—	++	
Sarcoma of scalp.....	152	—	—	+	+++	+	+++	++	—	++	++	++	—	++	
Normal .....	156	—	—	—	—	+++	+++	—	+	+	+	+	—	++	
Normal .....	148	—	—	—	—	—	++	—	—	—	—	—	—	—	
Normal .....	150	—	+	—	—	—	++	—	—	—	—	++	—	++	
Streptococemia .....	147	—	+	+	+	+	—	—	—	—	+	—	—	—	
Normal .....	155	—	+	—	—	+	+++	—	—	—	—	—	—	++	
Tuberculosis .....	158	—	—	+	—	+	+	—	+	+	+	—	—	+	
Fibroadenoma of breast...	151	—	++	+	+	—	+	—	—	—	—	++	—	—	
Endothelial sarcoma .....	153	—	+	++	—	++	++	—	+	—	—	+	—	—	
Carcinoma of breast.....	149	—	+	+	+	+	+	—	—	—	—	—	—	—	
Carcinoma of lung.....	142	—	+	+	+	++	++	++	—	+	++	++	—	++	
Carcinoma of rectum.....	140	—	+	+	—	+	+	—	—	—	—	—	—	—	
Saline control .....	—	+	—	—	—	+	+	—	—	—	+	+	—	+	

\* Of course those red blood cells which showed hemolysis in the saline controls are not counted in determining which sera are hemolytic. These hemolyses were due to the fact that the red cells used in these cases were more than twenty-four hours old.

other diseases. Thus the twenty-two cases with highly resistant red cells may be classified:

	Cancer.	Not Cancer.
With hemolytic serum.....	11	7
With non-hemolytic serum.....	1	3

But hemolytic serum does not invariably correspond to resistant red cells, as will be seen from the grouping of the forty-eight non-resistant red cells:

	Cancer.	Not Cancer.
With hemolytic serum.....	10	8
With non-hemolytic serum.....	6	24

Of the tumor cases only four can be said to have been in an early stage; these were Case 117, a small carcinoma of the sigmoid; Case 152, sarcoma of the scalp; Case 163, carcinoma of sigmoid; and Case 188, carcinoma of the pylorus. The other patients (which were such as are admitted to a general hospital for operation) showed either large tumors, metastases, glandular involvement, marked anemia, or other symptoms which prevented their cases from being regarded as early. Strangely enough the sera of the four early tumor cases were all strongly hemolytic.

The origin of the hemolytic property of the blood serum in disease is not yet clear. That it is not the specific product of any one disease process seems, from the variety of conditions in which it occurs, certain. Its probable source in the autolytic products of necrosis, in certain cases, has been pointed out by Weil. In seven of the carcinoma cases in the present series necrosis was observed in the pathologic findings. The serum of all seven of these patients was hemolytic, that of six of them markedly so. The same explanation is applicable to many, but not all, of the other diseases. In all of the seven cases of tuberculosis the tubercle bacilli had recently been demonstrated in the sputum, and there was therefore probably some breaking down of tissue. In the acute inflammatory and septic conditions, on the other hand, the well-known hemolytic products of the staphylococcus and streptococcus are to be considered. In some of the cases, such as those of diabetes, diffuse lipoma, chronic endocarditis, goiter, lead-poisoning, none of these explanations is adequate.

As a result of this work, the chief object of which has been to determine the value of isohemolytic reactions in diagnosis, we are forced to the unsatisfactory conclusion that the method is not at present to be relied on for diagnosis. While it is true that in a majority of cases of

malignant tumor this property of the blood is shown, it is also shown in a considerable proportion of other diseases. The most that can be said is that in a given case, if tuberculosis can be excluded, a strongly hemolytic serum is rather suspicious of carcinoma.

We desire to thank Dr. A. H. Harrigan for his kind assistance.

# THE INFLUENCE OF THE SOFT TISSUES OF THE ARM ON CLINICAL BLOOD-PRESSURE DETERMINATIONS

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A widespread impression exists that the degree of development of the musculature of the arm, or the size of the member, exercises considerable influence on blood-pressure readings made by the usual clinical methods, employing circular compression of the arm for the obliteration of the pulse. Von Recklinghausen's work demonstrated clearly that, with a sufficiently wide arm-piece, at least 12 cm., the latter factor could be entirely eliminated. Subsequently Müller and Blauel<sup>1</sup> made a critical study of this question, by comparison of clinical determinations with direct manometric measurements made in three patients during operation requiring the amputation of a hand. Their results showed an average reading with the broad cuff 9 to 10 mm. above the true systolic arterial pressure. They, of course, found very large errors with the narrow arm-piece and with Gärtner's method. Among their conclusions they state that, while the largest errors stand in direct relation to the width of the cuff, they are also partly dependent on the strength of the soft parts. This, so far as I know, is the only direct evidence for this contention that has yet been brought forward. Of evidence on the other side there is also a great paucity, the best being a case, reported by Hensen,<sup>2</sup> of marked muscular atrophy of the left side, the arm being entirely flaccid and of 22.5 circumference, while the right had a circumference of 25 cm. In this case the readings from the two sides were identical.

I desire to put on record two cases which, to me, demonstrate very clearly that such an influence of the soft parts does not exist, and that discrepancy between clinical blood-pressure estimations and direct manometric readings from the same limb, if found, must be explained either by resistance to compression of the arterial wall or by errors in the readings.

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1. Müller and Blauel: Zur Kritik des Riva-Roccischen und Gärtnerischen Sphygmomanometers. *Deutsch. Arch. f. klin. Med.*, 1907, xci, 517.

2. Hensen (H.): Beitr. z. Physiologie und Pathologie des Blutdrucks. *Deutsch. Arch. f. klin. Med.*, 1900, lxxvii, 443.

A man of 57, with chronic nephritis and marked cardiac hypertrophy, had sustained a fracture of the right elbow at the age of 16, which had resulted in complete ankylosis; in spite of this he worked all his life as a carpenter, and had an enormously developed left arm which measured 30 cm. in diameter; the right arm was absolutely flaccid, with very little muscle, and measured 21.5 cm. Both systolic and diastolic readings were identical in the two arms, the pressure being 300 mm. systolic and 180 mm. diastolic.

The second patient was a lumberman of 50, who had been in the woods most of his life, and was both muscular and obese, carrying 331 pounds without dyspnea. He had a very mild diabetes. His arm measured 39 cm. and gave the surprisingly low systolic reading of 115 mm.

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## EFFECT ON THE HEART OF EXPERIMENTAL OBSTRUCTION OF THE LEFT CORONARY ARTERY \*

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The literature on experimental obstruction of the coronary arteries in animals is not extensive, although dating back to the seventeenth century, when Chirac tied the coronary artery of a dog and noted that the heart stopped beating in one minute.

The next reference to this subject is Erichsen's<sup>1</sup> work in 1842, although previously to this Parry had published his observations on the relations existing between angina pectoris and sclerosis of the coronary arteries. Erichsen, recognizing obstruction of the cardiac vessels as a frequent cause of sudden death in man, ligated the coronary arteries near their origin in a pithed dog and reported gradually increasing bradycardia and finally cardiac standstill.

Panum,<sup>2</sup> in 1862, attempted to obstruct the coronary arteries by injecting a mixture of oil, wax, tallow and lampblack into the aorta. As the vessels were incompletely plugged, his results are not of any special value.

The next important contribution was by Bezold and Breymann,<sup>3</sup> published in 1867. After clamping the left coronary artery in a curarized rabbit, they observed slowing of the left ventricle with increasing arrhythmia, terminating in standstill, followed by fibrillar twitching.

Samuelson,<sup>4</sup> in 1881, reported some experimental work in which he compressed the left coronary artery in a curarized rabbit, bringing the left ventricle to a speedy standstill. He noted that the right ventricle did not cease beating as early as the left.

The same year Cohnheim and Schulthess-Rechberg<sup>5</sup> reported their exhaustive experimental work on curarized dogs. They found that

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\*From the Laboratory of Experimental Therapeutics, University of Chicago.

1. Erichsen (J.): Influence of the coronary circulation on the action of the heart. *London Med. Gaz.*, 1842, ii, 561.

2. Panum (P.): *Experimentelle Beiträge zur Lehre von der Embolie*. Virchow's *Arch. f. path. Anat.*, 1862, xxv, 308.

3. Bezold and Breymann: *Untersuchungen über die Herz- und Gefässnerven der Säugethiere*. *Untersuchungen a. d. physiol. Lab. zu Würzburg*, 1867, i, 256.

4. Samuelson (B.): *Ueber den Einfluss der Coronar-Arterien-Verschliessung auf die Herzaction*. *Ztschr. f. klin. Med.*, 1881, ii, 12.

5. Cohnheim (J.) and Schulthess-Rechberg: *Ueber die Folgen der Kranzarterienverschliessung für das Herz*. Virchow's *Arch. f. path. Anat.*, 1881, lxxxv, 503.

either main trunk of the left coronary artery might be clamped without immediate cardiac disturbance; within one or two minutes, however, slight irregularity of both sides of the heart appeared with decided slowing and a rapid fall in blood pressure, both ventricles stopping suddenly in diastole.

Porter,<sup>6</sup> in 1896, made the next important contribution. He dissected out and ligated the coronary arteries in curarized or etherized dogs and determined that the heart frequency was seldom changed when the ligation was not followed by standstill. His results differed from Cohnheim's in that ligation of a main trunk of the left coronary artery was not necessarily fatal, and that the fall in blood pressure was gradual, not abrupt. He noted that in those animals in which the ligation was followed by arrest there was a rise in the diastolic and a fall in the systolic intraventricular pressure, the output of the left ventricle steadily diminishing, both ventricles stopping simultaneously.

The work of Hirsch and Spalteholz,<sup>7</sup> published in 1907, is the last of the more important observations on this subject. Their experiments were undertaken with the purpose of determining whether the coronary arteries were terminal vessels in the sense of Cohnheim. They ligated the descending trunk of the left coronary in eight dogs and two apes, the only immediate effect being increased pulse frequency. After recovery from the operation, the animals showed no evidence of cardiac disturbance during the few weeks they were allowed to live. The autopsy showed a few small scattered areas of necrosis in the wall of the left ventricle, considerably less in extent than that supplied by the ligated vessel. In one animal that bled profusely the area of infarction was much larger. From this they conclude that the degree of infarction is dependent on the force with which the blood enters the coronary arteries; if good, the anastomosing vessels promptly supply the affected part. They deduce from these experiments the conclusion that in attacks of angina pectoris in man, the efficiency of the heart should be maintained in the highest possible degree in order to minimize the degree of infarction. On account of absence of evidence of cardiac disturbance during the life of the animals and the slight change found after death, the author concludes that a physiologic or functional anasto-

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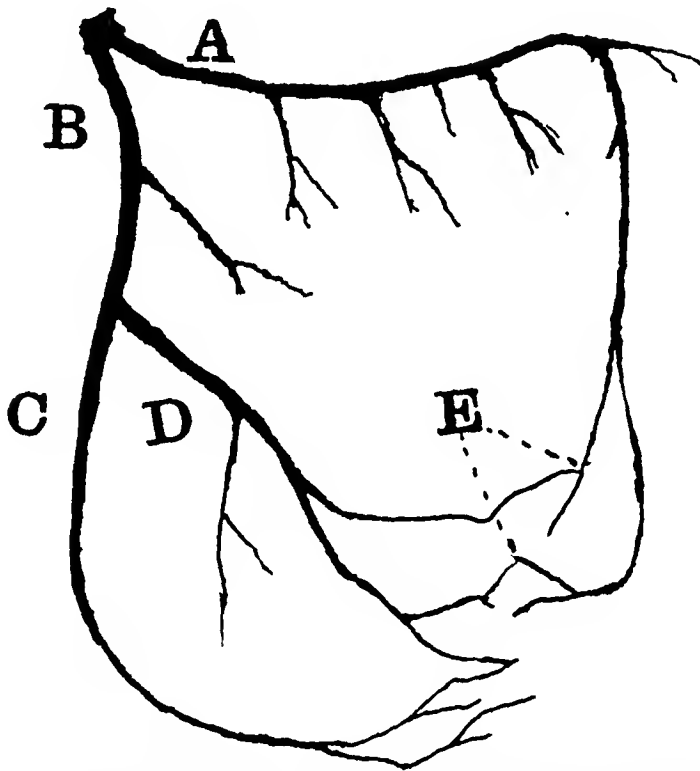
6. Porter (W. T.): Further researches on the closure of the coronary arteries. *Jour. Exper. Med.*, N. Y., 1896, i, 46.

7. Hirsch (C.) and Spalteholz: Coronararterien und Herzmuskel. Anatomische und experimentelle Untersuchungen. *Deutsch. med. Wochenschr.*, 1907, xxxiii, 790.

mosis exists in the coronary arteries in addition to the anatomic anastomosis previously described by Merkel.<sup>8</sup>

This short review of experimental work shows several points on which conflicting results have been obtained, especially the degree of ligation necessary to cause cardiac standstill and the manner in which it occurs. Our experimental study included a review of these points and a repetition of Hirsch's and Spalteholz's experiments. Before taking up these questions, a short anatomic description of the coronary arteries in dogs may be desirable.

The left coronary artery arises from the aorta usually by a single trunk, which immediately divides into two branches of about equal size,



Left coronary artery in the dog. A, circumflex branch; B, descending branch; C and D, main branches of the descendens; E, superficial anastomoses shown in injected specimens.

the circumflex and descendens. Not infrequently a common trunk is absent, the vessels arising from the aorta by separate orifices. The circumflex branch follows the auriculoventricular groove to the posterior intraventricular groove. Close to its origin a branch is given off to the left auricle, and along its entire course numerous short branches supply-

8. Merkel (H.): Zur Kenntnis der Kranzarterien des Menschlichen. Herzen. Verhandl. d. deutsch. path. Gesellsch., Jena, 1907. p. 127.

ing the upper and posterior portion of the left ventricle. The descending trunk follows the anterior interventricular groove to the apex. Within a few millimeters of the orifice a branch arises to supply the interventricular septum; this branch arises so close to the orifice of the main trunk that when the latter is ligated this branch usually escapes. About midway between its origin and the apex the descendens gives off a large branch which supplies the greater portion of the anterior and lateral surface of the left ventricle. A very few short vessels are given off to the right by the descendens. The right coronary artery is much smaller than the left, dividing in practically the same manner, except that it does not send off a branch to the interventricular septum.

All our experiments were performed on dogs. Ether was employed as an anesthetic. Artificial respiration was maintained by means of a bellows. Blood-pressure tracings were taken from the right carotid. The heart was exposed and the vessels ligated through a window in the left thorax. In a few instances the sternum was split or removed. The making of such a window caused a moderate fall in blood pressure: the shock, however, was slight. No attempt was made to dissect out the coronary artery, a round curved needle being passed beneath the artery and vein and both included in the ligature. The circumflex could be readily exposed and ligated by elevating the annicle. The entire operation, including ligation of the coronaries, could be performed with very slight loss of blood.

#### EXTENT OF LIGATION REQUIRED TO PRODUCE CARDIAC STANDSTILL

In twenty animals, either one main branch of the descendens was ligated (see illustration, C and D) or both main branches. Slight transitory arrhythmia appeared, usually attributable to the manipulation rather than the result of the ligation. Decided disturbance of the systole or fall in blood pressure was not observed. The pulse frequency was occasionally somewhat quickened, never slowed. All of these disturbances were of a temporary character, the heart promptly returning to normal. In the next series, of twenty-three animals, the circumflex was ligated at distances varying from 7 to 15 mm. from the orifice. Eighteen of these animals gave only moderate and temporary evidence of cardiac disturbance. There was a fall in blood pressure, occasional temporary arrhythmia and incomplete systole, with little disturbance in the pulse frequency and only slight dilatation of the left ventricle. After a few moments the heart returned to normal and so remained until the animal was killed or further ligation attempted. Five animals in this series developed more severe cardiac disturbances, the systole

became very incomplete and the ventricle showed marked dilatation. Three of the animals gradually recovered from these disturbances; the other two grew gradually worse, the disturbance of systole increased, the left ventricle became more and more dilated, the dilatation of the left ventricle being followed by dilatation of the left auricle and finally of the right auricle and ventricle. Cardiac standstill took place in two and five minutes, respectively.

Successive branches of the descendens were ligated in those animals recovering from the immediate shock produced by ligation of the circumflex. It was found that one and often both main branches of the descendens might be ligated without serious consequences. When, in addition to the circumflex, the main trunk of the descendens was ligated 25 mm. or less from its orifice, cardiac standstill promptly followed. Primary ligation of the descendens as near to the orifice as possible was not followed by any marked cardiac disturbance. Examination showed that in each instance the ligature was below the branch given off to the septum.

Comparing these results with those of previous experimenters, it is noted that Cohnheim reported cardiac standstill in every instance after ligation of either the descendens or circumflex. The heart stopped beating in 88 per cent. of Porter's animals after ligation of the circumflex and in 64 per cent. after ligation of the descendens. Only 8.7 per cent. of our animals died after ligation of the circumflex, and none after ligation of the descendens 10 mm. or less from its orifice. This difference in results can probably be explained by the difference in methods of anesthesia. Cohnheim used curare in all but two animals, and in these two morphin was the anesthetic. Porter also used either curare or morphin, except in a few instances in which the animal was anesthetized with ether, and he calls attention to the more frequent recoveries after ether.

#### MANNER IN WHICH STANDSTILL OCCURRED

The premonitory evidence of cardiac standstill was arrhythmia, incomplete systole of the left ventricle and gradual overfilling and dilatation of the left side of the heart, with later dilatation of the right auricle and ventricle. The carotid pressure very gradually fell to zero. Distention of the coronary veins marked the beginning of stasis in the right auricle. The left ventricle ceased beating first; the right ventricle continued pulsating irregularly somewhat longer. In a few instances the right ventricle continued to beat for several minutes after the left had ceased; this was especially noticeable when the animal had received

strophanthus. After the regular pulsations had ceased, fibrillar twitching was noted.

These observations are somewhat at variance with those of Cohnheim and Porter. Cohnheim reported sudden simultaneous stopping of both ventricles, the blood pressure falling abruptly to zero. Porter's results showing gradual stopping of the heart were in accord with our observations, but, like Cohnheim, he reported both ventricles stopping at the same time. As this latter observation is readily made, it is difficult to understand why in our animals the left ventricle ceased beating first; possibly the method of anesthesia was also responsible for the difference. Samuelson's results in this respect are in accord with ours. Although the left ventricle ceased beating first, pulmonary edema was never observed; this can be accounted for by the weakness of the right ventricle preventing a rise in the pulmonary pressure, apparently an essential to the development of acute experimental pulmonary edema.

#### EVIDENCE OF FUNCTIONAL CORONARY ANASTOMOSIS

In a series of twenty animals, Branch C or D (see Illustration 1) of the descendens was ligated and the animal allowed to live in order to determine whether functional cardiac disturbance might develop later. Only eight of the animals recovered, the others dying of sepsis. No immediate evidence of cardiac disturbance was noted, the animals behaving in a normal manner. Four of these dogs, showing no evidence of cardiac disturbance, were killed after five, ten, fourteen and thirty-five days, respectively. In each animal a small area of infarction could be detected, but no evidence of dilatation of the chambers. The other four animals died at the end of twenty-six, forty-two, forty-five and ninety days, respectively. These animals were in apparently normal health a few hours before death, the symptoms developing acutely. The signs and symptoms preceding death were observed in only two animals, the others being found dead in their cages. Restlessness and intense dyspnea were the chief premonitory symptoms. One animal lived above two hours after the first symptoms were noted. The suffering of the other animal was so intense that chloroform was used to hasten death. The hearts of these four animals were very much dilated, especially the left ventricle. Peripherally from the ligature there was a circumscribed area of necrosis 0.5 to 1 cm. in diameter, where the heart wall was thinned to one-fourth its normal thickness. From the signs, symptoms and autopsy findings it appears highly probable that these animals died from acute cardiac insufficiency.

Merkel and Hirsch and Spalteholz, each by a somewhat different method, have shown that the terminal branches of the coronary arteries anastomose freely. Hirsch and Spalteholz, after ligation of a single trunk of the left coronary artery, thought that they had demonstrated that this anastomosis was sufficient to maintain the nutrition of the heart muscle. Their animals did not show any evidence of cardiac disturbance in the rather short time they were allowed to live after the ligation. If they had allowed a longer period of time to elapse, it is highly probable that cardiac disturbance would have developed as it did in our animals, especially as they ligated the main trunk of the descending, whereas we ligated only a branch of the same.

#### EFFECT OF DRUGS ON THE CARDIAC DISTURBANCE INDUCED BY LIGATION OF THE CORONARY ARTERIES

After some experience we were able to determine the extent of ligation necessary to cause marked disturbance of the left ventricle from which recovery would yet take place, and also the necessary amount of obstruction to bring about a fatal termination. These points having been determined, drugs could be employed to see if the changes following ligation could be modified. Tincture of *strophanthus* in 0.1 c.c. doses intravenously was first tried. It was shown, if the drug was used at a time when the arrhythmia was marked, the left ventricle and auricle dilated and the cardiac pressure very low, in one instance 18 mm. of mercury, that the systole improved, the dilatation gradually disappeared and the blood pressure returned to its previous level. In case the administration of the drug was delayed until the pulsation of the left ventricle had almost ceased, recovery did not follow. It was also determined that an animal which had received a dose of *strophanthus* could endure much more extensive ligation of the coronary arteries without serious consequences than an untreated animal. Morphine in 15 mg. doses to a 10-kilo dog acted unfavorably, increasing the readiness with which disturbance could be produced by ligation. This is in accord with Porter's findings. The various vasodilators were used, but without benefit, as might be expected where the obstruction was not the result of spasm.

We are not justified, however, from these therapeutic experiments, in drawing conclusions regarding the treatment of angina pectoris in man. Obviously the element of pain and previous myocardial degeneration do not enter into the problem in dogs. Not every attack of angina pectoris is due to actually complete obstruction of a coronary artery, although

von Leyden's<sup>9</sup> careful clinical and autopsy studies show the great frequency with which a thrombus or embolus is responsible for the attacks. His studies would indicate that the importance of vascular spasm as an etiologic factor in the attacks has been probably overrated. When we consult clinical experience, we find that in England and America Branton's teaching on the importance of vascular spasm has had much influence and consequently the vasodilators have been extensively used. In Germany the vasodilators are not generally recommended in the treatment of an attack. Leyden says he has seen only a single case in which amyl nitrite had the prompt effect described by Branton. Romberg<sup>10</sup> reports that he has seen only one patient relieved promptly by amyl nitrite, and, although he highly recommends nitroglycerin to ward off attacks or check them in their incipency, in the height of an attack he considers it of little value. In the writer's limited experience, prompt relief has never been observed after the use of nitroglycerin or amyl nitrite. The tendency to spontaneous recovery from an attack may be responsible for some of the beneficial results attributed to the vasodilators. If vascular spasm is responsible for the attack the relief afforded by amyl nitrite should be immediate, and that from the use of nitroglycerin by mouth should be afforded within two to five minutes, as its maximum effect is reached within this period of time. Improvement taking place ten to fifteen minutes after the administration of either of these remedies is probably due to other causes than the drug. Many of the German writers recommend cardiac stimulants, as caffeine, camphor and digitalis. The actual merits of these two widely different forms of treatment can be properly discussed only when we know the rôle played by spasm in inducing the attack. Of some therapeutic interest is the lessened cardiac disturbance after obstructions in those animals under the influence of strophanthus. It is possible that the danger of serious consequences during an attack of angina pectoris may be lessened by giving a patient subject to these attacks small doses of strophanthus.

#### CONCLUSIONS

Either main trunk of the left coronary artery may be ligated without seriously disturbing the heart.

In the cases reported, ligation of the descendens 25 mm. or less from its orifice, after previous ligation of the circumflex, always caused cardiac standstill. The left ventricle stopped beating first.

9. Von Leyden (E.): Ueber die Sclerose der Coronararterien und die davon abhängigen Krankheitszustände. *Ztschr. f. klin. Med.*, 1883, vii, 459.

10. Romberg (E.): *Krankheiten des Herzens und der Blutgefässe*, vol. 2, Stuttgart, 1906, Ferdinand Enke.



When either of the two main branches of the descendens is ligated and the animal allowed to recover, no evidence of cardiac disturbance is apparent for a period varying, in our experiments, from one to three months, when very acute symptoms of cardiac insufficiency develop which rapidly prove fatal.

The previous administration of strophanthus permits much more extensive ligation of the coronary arteries without serious consequences.

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## SERUM DISEASE \*

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After diphtheria antitoxin came into general use in the treatment of diphtheria in 1894, the occurrence of exanthems, joint pains, etc., following the injection began to be reported. Various observers noted a larger or smaller proportion of such reactions among the cases coming under their care, and it was generally agreed that the reactions were a source of annoyance rather than of danger. Gradually there have accumulated reports of cases in which injections of serum have been followed by alarming symptoms, and in very exceptional instances even by death. During the past three years many workers have reported the results of investigations on the effects on animals of injections of alien blood serums. Some of the obscure phenomena associated with the toxic action of horse serum in man are illuminated by these investigations. It was thought that it might be profitable to study the records of serum reactions as they have occurred in the diphtheria wards of the Cook County Hospital during the past two years, relating some of the more interesting cases and discussing in a brief manner some of the questions arising from such a study.

It is a pleasure to express publicly my appreciation of the uniform generosity of my colleagues, Dr. W. L. Baum and Dr. A. M. Cameron, in allowing the use of cases occurring in their services on this and other occasions.

From Nov. 1, 1906, to Dec. 25, 1908, there were admitted to the contagious wards, with a clinical diagnosis of diphtheria, 956 patients, all of whom were given injections of diphtheria antitoxin. Serum reactions were observed in 236 cases, i. e. 24.6 per cent. of all cases in which injections were given. This, however, does not represent the total reactions among these patients, since 264 patients died or were discharged after being under observation from one to nine days and before the reaction would have appeared in many of them. If we deduct these cases from the total number of patients admitted, we have 692 cases left on which to compute the real number of serum reactions likely to follow injections of antidiphtheric serum. Of these 692 cases, observed for ten days or more, 236, or 34.1 per cent., exhibited reactions. If all

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\*From the Cook County Hospital and the Memorial Institute for Infectious Diseases, Chicago; read at the West Side Branch of the Chicago Medical Society, Feb. 18, 1909.

the cases had been observed for three weeks the total number showing reactions would be slightly increased. Statistics from hospitals where considerable numbers of cases have been observed have given the proportion of reactions from 14 to 50 per cent. As I shall show, the number of reactions will vary with the particular serum used, and especially with the amount of serum injected. In hospitals such as ours, where a

TABLE I.—FREQUENCY OF SERUM REACTIONS WITH DIFFERENT QUANTITIES OF SERUM

Total Amount of Serum.	Cases Showing Reaction.	Cases Observed 10 Days or More Showing No Reaction.	Total Cases.	Per Cent. of Cases Showing Reaction.
1-9 c.c.....	9	73	82	10.9
10-19 c.c.....	52	137	189	27.5
20-29 c.c.....	40	100	140	28.5
30-39 c.c.....	28	47	75	37.3
40-49 c.c.....	19	26	45	42.2
50-59 c.c.....	15	16	31	48.3
60-69 c.c.....	17	23	40	42.5
70-79 c.c.....	14	7	21	66.6
80-89 c.c.....	8	12	20	40.0
90-99 c.c.....	7	2	9	77.7
100-109 c.c.....	4	5	9	44.4
110-119 c.c.....	3	1	4	75.0
120-129 c.c.....	1	1	2	50.0
130-139 c.c.....	4	2	6	66.6
140-149 c.c.....	3	1	4	75.0
150-159 c.c.....	2	1	3	66.6
160-169 c.c.....	2	2	4	50.0
170-280 c.c.....	8	0	8	100.0
Total.....	236	456	692	34.1

large proportion of late and severe cases are treated, and where many laryngeal cases are admitted, the amount of serum administered is often large, and the occurrence of reactions correspondingly frequent.

There are several factors which enter into the determination of the frequency of serum reactions. One of these is the individual susceptibility, which varies greatly. Another is the toxic factor of the horse serum. Some serums provoke a greater proportion of reactions than others, and the serum from the individual horse varies in this respect

TABLE II.—THE NUMBER OF CASES OF SERUM REACTION FALLING ON EACH DAY AS RECORDED BY VALDÉ'S APPARATUS.\*

	Day.	No. of Cases.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	Total
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	Total
Author's Cases.....		1	5	9	16	22	30	25	30	26	20	6	7	4	7	3	1	1	2	.....	1	.....	1	.....	22	
Von Pirquet and Schick.....	"	.....	2	.....	3	.....	7	7	16	16	9	6	6	5	3	3	1	1	.....	.....	.....	.....	.....	.....	67	
Currie.....	"	.....	.....	1	6	11	14	26	35	57	41	18	8	15	5	9	6	3	1	2	.....	.....	1	.....	257	
Von Rittershain .....	"	2	1	11	11	4	11	2	2	.....	4	2	2	3	1	.....	1	.....	.....	.....	.....	.....	.....	.....	77	
Hirtung.....	"	6	1	8	5	2	2	7	2	.....	6	13	2	3	2	1	.....	.....	.....	1	0	2	.....	1	64	
Von Bokay .....	"	.....	2	4	3	6	8	11	9	14	12	5	5	4	2	3	3	.....	.....	.....	.....	.....	.....	.....	91	
Daut .....	"	1	.....	2	1	.....	1	3	1	2	.....	1	2	4	1	.....	.....	.....	1	1	.....	.....	.....	.....	21	
Total .....	"	13	11	35	45	45	73	81	95	117	92	51	84	38	21	19	12	5	4	4	1	2	2	1	801	

\* With the exception of V. Rittershain, all authors counted from the first injection. This author counted from the last injection and consequently his reactions appear to have occurred earlier than the others.

at different bleedings. Fresh serum is, as a rule, more prone to give rise to reactions than are serums that have been longer preserved before being used. Both of these factors have been spoken of by previous authors. A third factor, which is the most important one in determining the occurrence of serum reactions, is the quantity of serum injected. We have tabulated the quantity of serum administered in each of the 692 cases which were under observation for ten days or more (Table 1). It will be observed that the percentage of reactions increases with the

TABLE III.—NUMBER AND PER CENT. OF SERUM REACTIONS AT VARIOUS INTERVALS AFTER DIFFERENT TOTAL QUANTITIES OF SERUM

Dose.	1-3 Days.	4-6 Days.	7-9 Days.	10-12 Days.	13-15 Days.	16-22 Days.	Total Cases.
1 to 49 cc....	8 5.6%	43 30.4%	57 40.4%	22 15.6%	8 5.6%	3 2.1%	141
50 to 109 cc...	10 17.2%	16 27.2%	18 31.0%	8 13.6%	4 6.8%	2 3.4%	58
110 to 280 cc.....	.....	7 31.5%	8 36.0%	4 18.0%	2 9.0%	1 4.5%	22

TABLE IV.—NUMBER AND PER CENT. OF SERUM REACTIONS AT VARIOUS INTERVALS AFTER DIFFERENT NUMBERS OF INJECTIONS

No. of Doses.	1-3 Days.	4-6 Days.	7-9 Days.	10-12 Days.	13-15 Days.	16-22 Days.	Total Cases.
1.....	3 6.3%	16 34.0%	14 29.7%	9 19.1%	2 4.2%	3 6.3%	47
2.....	2 2.8%	18 26.0%	32 46.3%	11 15.9%	6 8.6%	.....	69
3.....	4 9.5%	17 40.4%	15 35.7%	5 11.9%	1 2.3%	.....	42
4.....	2 10.5%	2 10.5%	8 42.0%	4 21.0%	3 15.7%	.....	19
5 or more....	5 11.3%	16 36.3%	14 31.8%	5 11.3%	2 4.5%	2 4.5%	44
2 or more....	13 7.4%	53 30.4%	69 39.6%	25 14.3%	12 6.8%	2 1.1%	174

quantity of serum given. In the series receiving the larger doses, the relative small number of cases deprives the relative percentages of much value. Of the patients receiving less than 10 c.c. of serum, 10.9 per cent. showed reactions; of those receiving from 10 to 30 c.c., 27.9 per cent. showed reactions; of those receiving from 30 to 50 c.c., 39.1 per cent. showed reactions; of those receiving from 50 to 100 c.c., 50.4 per cent. showed reactions, and of those receiving over 100 c.c., 67.5 per cent. showed reactions. The relative infrequency of reactions after small

doses of serum is well shown by a study of a large series of cases of scarlet fever, which were given an immunizing dose of 1,000 units on admission to the hospital. These cases were under observation from four to six weeks. Of 894 patients receiving a single injection of 1,000 units, 51, or 5.7 per cent., developed a reaction. Of 21 measles patients similarly immunized, only one developed a very mild reaction.

The increased frequency of reactions with increased dosage has been observed by practically all authors. Von Rittershain<sup>1</sup> observed 81.4 per cent. of all cases of reaction in the cases receiving 7 c.c. or more of serum. Daut<sup>2</sup> noted reactions in 5.4 per cent. of patients receiving from 2 to 15 c.c., and in 32.1 per cent. of patients receiving from 20 to 60 c.c. of serum. Von Pirquet and Schick<sup>3</sup> observed reactions in 85 per cent. of the cases receiving from 100 to 200 c.c. of serum.

The interval between the injection and the appearance of the reaction varies from a few minutes to twenty-three days. Table 2 shows the number of cases falling on the different days after the injection. The table includes for comparison the observations on this point by several authors. Of our 222 cases, in which the time of appearance of the reactions is definitely recorded, 189, or 85.2 per cent., occurred before the eleventh day. Of the 801 cases collected in our table, 607, or 75.7 per cent. occurred before the eleventh day. It will be observed that the largest number of cases fell on the days from the sixth to the tenth. The length of the incubation appears to be independent of the number of injections and of the total quantity of serum. Tables 3 and 4 show this quite distinctly. This has been insisted on by Currie<sup>4</sup> and Goodall.<sup>5</sup>

During the past year we have used antitoxin precipitated according to Gibson's methods in a considerable number of cases. This incidence of reactions after its use is not different from that following the injection of whole horse serum in corresponding bulk. This is in accord with the observation of Rosenau and Anderson,<sup>6</sup> that "refined antitoxic serum precipitated and dialyzed in accordance with the Gibson method is quite as toxic, bulk for bulk, as the untreated serum from which it has been obtained."

#### CLINICAL MANIFESTATIONS

The term "serum disease" has been applied by von Pirquet and Schick to the reaction which follows the injection of horse serum. This

1. Von Rittershain: *Jahrb. f. Kinderh.*, 1902, iv, 512.

2. Daut: *Jahrb. f. Kinderh.*, 1897, xlv, 289.

3. Von Pirquet and Schick: *K. K. Universitäts-Kinder-Klinik, Vienna*, 1905.

4. Currie: *Jour. Hyg.*, 1907, vii, 35.

5. Goodall: *Jour. Hyg.*, 1907, vii, 607.

6. Rosenau and Anderson: *Bull. 26, Hyg. Lab. U. S. P. H. and M. S.*, 1907.

has a decided advantage over the earlier terms, such as "antitoxin rash," "serum exanthems," etc. The former term is particularly inappropriate, as antitoxin has nothing to do with the phenomena. Many observations have shown that the reaction is entirely dependent on the injected horse serum, and that it is produced equally well by normal horse serum and other therapeutic serums. To describe the reaction by speaking of the rash or exanthem is also inaccurate, since the cutaneous manifestation is only one of the signs of disturbed activity following the introduction of the foreign serum.

I shall first consider the reaction which follows a primary administration of serum, and afterward the reaction observed after secondary injections, which are given after an interval of some days or more.

#### REACTION FOLLOWING A PRIMARY INJECTION OF HORSE SERUM

The interval between the time of injection and the appearance of toxic symptoms, i. e., the period of incubation, varies in man from a few minutes or hours to three weeks or more. Aside from a little local soreness at the site of injection for twenty-four hours, the patient presents no ill effects from the injection. At the end of this incubation period the symptoms of intoxication become suddenly manifest, and after a variable period of a few hours or several days they disappear, leaving no permanent ill effects. Slight redness and itching at the site of injection and a little swelling of adjacent lymph glands may precede the appearance of more pronounced symptoms. The prominent manifestations are fever, skin eruptions, edema, swelling of lymph glands, leukopenia and joint symptoms. These occur in various combinations, one being most prominent in one case, another in another case. All may occur in a given case or most may be absent.

In a considerable number of cases the reaction remains local throughout (Cases 1, 2 and 3). Von Rittershain, Daut and Hartung<sup>7</sup> observed local reactions in about one-fourth of their series. It has been generally noticed that local reactions occur earlier than general ones, and that they usually run an afebrile course, with little or no general disturbance. Occasionally a local reaction develops almost at once after the injection and corresponds very closely in its course to the cases of "immediate" local reaction, of which we shall speak later. I have included among the appended illustrative cases such a case of severe local reaction with fever and general disturbance (Case 1). Von Pirquet and Schick de-

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7. Hartung: *Jahrb. f. Kinderh.*, 1896, xlii, 72.

scribe a similar case, but are skeptical as to its being properly included in this class.

It is not unlikely that some of the cases of local swelling with pain which follow an injection of serum in a short time are instances of specific local reaction.

After a primary injection I have several times observed, first, a rather early local reaction, and after an interval of several days a general reaction (Cases 4 and 5). Cases of this variety have been mentioned by von Rittershain.

I have never seen a case of immediate general reaction, which rarely occurs after a primary injection. Here belong cases that are quickly fatal, the patients dying in five to ten minutes after the injection; Rosenau and Anderson<sup>8</sup> in 1906 collected nineteen instances recorded in medical literature. Recently Gillette<sup>9</sup> has collected 28 cases of very severe general reaction, coming on immediately after the injection of horse serum, 15 of which were fatal. The symptoms are very similar in all, in some certain phenomena being more pronounced than in others. A few minutes after the injection there appears an irritation of the skin, especially about the face, dyspnea, cyanosis, violent urticaria and edema, especially of the face. Frothy fluid may escape from the respiratory passages, and there may be extreme swelling of the mucous membranes of the throat and larynx. Death occurs with stoppage of respiration, the heart continuing to beat some time longer. Of Gillette's cases, 18 were in persons with a distinct history of asthma, 9 of whom died. In some of the patients the asthmatic attacks were provoked by being about horses.

The most typical cases of serum reaction begin with local swelling at the site of injection, the surrounding skin showing urticarial wheals and erythema. Soon the urticaria becomes general over the body, accompanied by severe itching (Cases 6 and 7). Fever often precedes and accompanies the exanthem and sometimes persists after its disappearance. The lymph glands adjacent to the site of injection show enlargement and may be tender to touch, and there may be enlargement of the lymph glands throughout the body.<sup>10</sup> With the general urticaria the patient is restless, irritable or may be drowsy.

The urticarial lesions may become confluent, leading to general edema of the involved skin. This is especially noticeable on the face.

8. Rosenau and Anderson: Bull. 29, Hyg. Lab. U. S. P. H. and M. H. S. 1906.

9. Gillette: Therap. Gaz., 1909, XXXIII, 159.

10. Von Pirquet and Schick state that swelling of the other organs is more common only than swelling of the lymph glands.



where the loose tissues of the eyelids and lips may be so swollen as completely to disfigure the features. The urticaria usually disappears as suddenly as it comes, and the fever and general ill feeling usually subside with it. It is common for the urticaria to disappear almost completely for several hours and return again. This may be repeated several times. In one of the cases observed (Case 10) an outbreak of urticaria occurred on the sixth day, lasting a few hours. After a free interval urticaria again developed on the thirteenth day and persisted quite constantly for three days. The urticarias were usually of short duration, only a few lasting three or four days. In 1 case urticaria persisted five days, in 2 cases six days, and in 1 case seven days. Von Rittershain did not observe a longer persistence of the eruption than five days, but Hartung and Daut noted several such cases. The larger the quantity of serum administered the more severe are the symptoms apt to be. A much larger proportion of severe reactions occurred among the patients receiving the larger quantities of serum. Occasionally a very severe reaction occurred after the injection of a small quantity of serum, 15 c.c. or less.

Fever is an inconstant symptom. It was present in over half the cases observed by von Rittershain, Hartung and Daut. We have several times noted a prodromal fever the day preceding the eruption, as previously described by von Rittershain (Case 9). In accord with his observations, the fever more often came at the same time as the skin eruption. Cases of severe urticaria may run afebrile courses (Case 8). Von Pirquet noted that high fever of short duration was often seen after injections of small quantities of serum. He ascribes the duration and intensity of fever partly to the quantity of serum administered and partly to the individual susceptibility.

Pains in the joints may occur as the only symptom of serum intoxication, but usually they precede, accompany or follow other manifestations. Hartung noted joint symptoms in 10 out of 68 cases of serum disease. More or less joint symptoms were noted in about 20 per cent. of our cases. In some the pain was very severe and persistent; in others very slight and transient, and in some cases a stiffness only was complained of. The pains are spontaneous, increased by motion and sometimes by touch. The severity of the pain is usually in marked contrast to the limited objective findings. After one to three days the pains disappear, leaving the joints without permanent alteration. In our experience, swelling of the affected joints is unusual. Von Rittershain observed swelling of the joints in a single case. In Hartung's 10 cases with

joint pains, swelling was present in 8. In one of his cases there was much effusion into the knee joint. The joints most often involved are those of the hand, including the metacarpophalangeal joints. Next in frequency are the knee joints. Any of the joints may be involved, and often several are affected simultaneously or in succession. Effusions into serous cavities are not frequent. Rosenhaupt<sup>11</sup> has recorded a case in which abundant pericardial effusion accompanied a severe reaction, which terminated in recovery.

Von Pirquet and Schick have shown that a general edema can be demonstrated at the time of the serum reaction by weighing the patient. The weight rises with the appearance of the symptoms of the reaction and again falls with their subsidence. The edema of the face and sometimes of the hands is quite apparent in severe cases.

A slight transient albuminuria is said by von Pirquet and Schick to occur but rarely. The urine is often reduced in quantity.

A leukopenia has also been noted by them.

Of the skin eruptions which may develop, aside from urticaria, a simple erythema is most common (Cases 11 and 12). This may be limited to the skin about the site of injection, or it may extend over a large part of the body. It is often associated with urticarial lesions, and may be accompanied by fever. The redness disappears on pressure, and is usually quite transient, lasting from one to three days.

Less frequently are observed cases of exanthem, which are very suggestive of the eruption of measles (Case 13). Two such cases were observed in our series. One was accompanied by fever and one was afebrile. These cases are differentiated from measles by the lack of catarrhal symptoms, the absence of Koplik's spots in the mouth and the abrupt fading of the rash. Berg<sup>12</sup> says that catarrhal symptoms are sometimes shown in cases of serum reaction.

The true scarlatinal form of exanthem is very rare. We have records of a single typical case (Case 14). The rash appeared on the ninth day with a temperature of 101 F., and the rash over the body was indistinguishable from that of scarlet fever. Angina and the characteristic appearance of the tongue were absent. The fever fell the second day and no desquamation followed. In cases of this type a differential diagnosis is very difficult, especially in connection with diphtheria in which the throat is still red. If joint pains appear, the

11. Rosenhaupt: *München. med. Wochenschr.*, 1905, lvi, 2049.

12. Berg: *Med. Rev.*, 1898, lili, 865.

eruption, they are an aid in diagnosis, since the joint complications in scarlet fever are not apt to occur during the acute eruptive stage.

Of the erythema multiforme and exudativum, which occur in association with the serum reaction, we have observed but 3 cases, 2 of the former and 1 of the latter. They are among the rare manifestations of serum intoxication.

The mucous membranes are usually unaffected, but in some cases there is swelling of the tongue and the lining of the throat. The involvement of the respiratory mucous membrane is evidenced by cough and hoarseness (Case 15). Mucous membranes which have been the seat of the diphtheritic process are more prone to exhibit swelling at the time of the serum reaction. I have noticed this in a marked degree in a case of severe and extensive pharyngeal diphtheria (Case 16). The local signs had nearly disappeared when manifestations of the serum intoxication made their appearance. Simultaneously there developed marked swelling of the mucous membranes of the throat previously involved in the diphtheria, and this subsided as the other symptoms of the serum reaction cleared up. In 2 or 3 cases of laryngeal diphtheria we have noted similar phenomena (Case 17). After all laryngeal symptoms had been absent several days, with the onset of an urticaria the children again became very hoarse and croupy, but in no case was there sufficient obstruction to require intubation. Cases of this sort were first reported by Mya.<sup>13</sup> In one of his cases the preceding laryngeal inflammation was catarrhal, and in one an immunizing dose of 500 units was followed by a severe serum reaction during which alarming symptoms of laryngeal obstruction appeared. He speaks of the condition as a sort of "urticaria of the mucous membrane of the larynx" and a "hypoglottic edema." A similar case was related by von Pirquet and Schick.

Disturbance of the stomach, as shown by local discomfort, nausea and vomiting, were observed several times. Similar symptoms have been observed by Hartung and others. In one of our cases of reaction following a secondary injection, nausea and vomiting were associated with a very troublesome urticaria, and jaundice appeared, to clear up quite rapidly after the reaction subsided. Hartung noted that constipation often accompanied the serum reaction and less frequently diarrhea. In an infant he observed catarrhal enteritis. In two older children he saw an enteritis, once with muco-bloody stools, and once with serous stools containing blood-stained mucous particles.

More or less general disturbance accompanies all cases of severe serum reaction. Adults some time complain of headache, backache and

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13. Mya: *Monatschr. f. Kinderh.*, 1903, ii, 527.

severe aching in the muscles. In the more severe cases there is a considerable degree of prostration, with tendency to fainting.

I have not observed desquamation after the eruptions, but such has been described. Even after the cases of scarlatiniform eruption the desquamation is fine, and not like that which follows scarlet fever.

#### CASES ILLUSTRATING SOME OF THE REACTIONS FOLLOWING PRIMARY INJECTIONS OF SERUM

*CASE 1.—Primary injection, typical immediate local reaction, coming on in two hours.*

*History.*—The patient, a man, aged 31, with the exception of typhoid fever eight years before this illness, was very well since 10 years of age. He was subject to urticaria in childhood. He had never had rheumatism or asthma; had never received any injections of any sort. The patient was a very intelligent man, and previous sensitization by horse serum could be absolutely excluded.

*Injection of Serum.*—Nov. 8, 1908, at 2 p. m., 1 c.c. of antidiphtheria serum was injected beneath the skin of the forearm as a prophylactic measure after exposure to diphtheria. The serum used was whole horse serum.

*Reaction.*—At 4 p. m. the entire skin of the forearm was red and swelling was present at the site of injection. At 6 p. m. urticarial wheals appeared on the arm, and recurred for two days. They were mostly on the forearm, a few occurring above the elbow. No lesions occurred on other parts of the body. The swelling of the forearm increased until the evening of November 9, when there was great swelling of the entire forearm, extending a little on the back of the hand. The skin overlying the swollen parts was intensely red. During this time there was extreme itching, aggravated with each new appearance of urticarial wheals. The arm felt stiff and clumsy; there was no acute pain, but there was limited tenderness to pressure. No glandular alterations were noted. During this time there were no general disturbances.

Nov. 10, 1908: In the morning the patient went to work feeling well, except for stiffness in the swollen arm. At 10 a. m. he suddenly developed a temperature of 102 F., with severe headache, vomiting, and a feeling of general weakness. At 1 p. m. he staggered as he walked home and felt extremely prostrated. From 2 to 5 p. m. he slept, and on awaking the fever had subsided, but a feeling of great weakness persisted.

Nov. 11, 1908: The patient was about, but felt very weak.

Nov. 12, 1908: The patient felt well.

*Reaction.*—On Nov. 26, 1908, twenty-two hours after the injection, there developed headache and a painful swelling at site of injection, which disappeared in two days. The overlying skin was erythematous. No other symptoms developed.

*CASE 3.—Primary injection, local reaction on sixth day.*

*Injection of Serum.*—A boy, aged 7, was given 2 c.c. antidiphtheria serum on Jan. 13, 1908, for the purpose of immunization after exposure to diphtheria.

*Reaction.*—On Jan. 19, 1908, at the site of injection, there was erythema of an area of the size of the hand; no swelling. On Jan. 20, 1908, there was an urticaria about area of erythema. The next day the patient was better, and no other symptoms followed.

*CASE 4.—Primary injection, local swelling and erythema in nineteen hours and general urticaria on the sixth day.*

*Injection of Serum.*—A girl, aged 5, had diphtheria. On Jan. 1, 1907, 25 c.c. of antidiphtheria serum were given in two doses at 1 and 6 p. m.

*Reaction.*—On Jan. 2, 1907, 8 a. m., at the site of the injection was a tender swelling, with erythema of the overlying and surrounding skin, which subsided in two days. On Jan. 7, 1907, there were a few urticarial lesions scattered over the entire body. On Jan. 8, 1907, there was marked general urticaria.

*CASE 5.—Primary injection, local reaction in twenty-four hours, erythema on the tenth day.*

*Injection of Serum.*—A girl, aged 9, had diphtheria. On Jan. 17 and 18, 1906, she was given 40 c.c. of antidiphtheria serum in three doses.

*Reaction.*—Twenty-four hours after the first injection there appeared tender swellings at the site of injections with erythema of skin over and about them, which disappeared in two or three days. On Jan. 27, 1906, she had headache, diffuse erythema over chest and slight erythema in a few other places.

*CASE 6.—Primary injection, local reaction with some general urticaria on the sixth day.*

*Injection of Serum.*—A girl, aged 8, was given 2 c.c. antidiphtheria serum on Jan. 13, 1908, for the purpose of immunization after exposure to diphtheria.

*Reaction.*—On Jan. 19, 1908, there was an elevated red area, six inches in diameter, at the site of the injection. The adjacent lymph glands were enlarged and tender. There were a few urticarial lesions on the legs and lips. The following day the lesions were less marked and rapidly declined.

*CASE 7.—Primary injection, local reaction on the sixth day, followed by very severe general urticaria lasting seven days.*

*Injection of Serum.*—A woman, aged 23, had diphtheria. On Oct. 13, 1907, she was given 4 c.c. of antidiphtheria serum in a single dose. On Oct. 19, 1907, in the afternoon, painful swelling appeared at the site of injection with slight adjacent urticaria. On Oct. 20, 1907, there was a slight urticaria on the back and continuance of local reaction. On Oct. 21, 1907, there was no fever; slight local and general urticaria. The patient complained of a "smothering sensation." On Oct. 22, 1907, at 4 p. m., there was marked urticaria, especially about the larger joints of extremities. On Oct. 23 to 26, 1907, there was severe general urticaria coming and going. On Oct. 27, 1907, the urticaria was slight and less troublesome. On Oct. 28, 1907, the urticaria was absent and did not return. The entire course was afebrile.

*CASE 8.—Primary injection, general urticaria on sixth day, with considerable general disturbance.*

*Injection of Serum.*—A boy, aged 11, had diphtheria. On Jan. 9, 1907, he received 12 c.c. of antidiphtheria serum.

*Reaction.*—On Jan. 15, 1907, 8 a. m., there was urticaria over the entire body; the temperature was 98.6 F., the pulse 92. At 2 a. m. the patient had headache, nausea, dizziness. Urticaria came and went during the three next days with some ill feeling. On Jan. 19, 1908, the patient had general urticaria, a fainting attack on rising, and his pulse was weak. The next day the urticaria was absent and did not occur, and improvement was rapid from this time.

*CASE 9.—Primary injection, severe general reaction on ninth day, preceded by fever.*

*Injection of Serum.*—A girl, aged 18, had diphtheria. On Oct. 2, 1908, 10 c.c. antidiphtheria serum were administered, and on Oct. 3, 1908, 20 c.c. of the same.

*Reaction.*—On Oct. 11, 1908, the patient's temperature was 100.4 and the pulse 120; the patient was very restless. There was no eruption. On Oct. 12, 1908, the temperature was 101.6 F., the pulse 120; there was severe general urticaria. The patient complained much of pain in muscles; was very restless. On Oct. 13, 1908, the temperature was 101.8 F., the pulse 116, the urticaria severe, the face flushed, and the patient very restless. On Oct. 14, 1908, the urticaria was less violent. The patient's temperature was 99.2 F., pulse 100; there was marked prostration. On Oct. 15, 1908, there was no urticaria. The temperature was 98.4 F., pulse 72. From this time on improvement was rapid.

*CASE 10.—Primary injection, urticaria on the sixth day, recurring on the thirteenth day.*

*Injection of Serum.*—A girl, aged 2, had laryngeal diphtheria. On Dec. 25, 1907, 20 c.c. and on Dec. 26, 1907, 8 c.c. of antidiphtheria serum were injected.

*Reaction.*—On Dec. 31, 1907, there was a mild general urticaria lasting a few hours. From this time the patient was entirely free from any signs of reaction until Jan. 7, 1908, when a moderate general urticaria appeared and persisted for four days.

*CASE 11.—Primary injection, erythema on third day, followed later by pains in joints and muscles and still later by general urticaria.*

*Injection of Serum.*—A man, aged 22, had diphtheria. On Nov. 1, 1908, 20 c.c. of antidiphtheria serum were injected, and on Nov. 2, 1908, 40 c.c. in two doses.

*Reaction.*—On Nov. 4, 1908, there was erythema over the abdomen and arms. On Nov. 5, 1908, the erythema was extending over body. There was pain in joints and muscles. On Nov. 15, 1908, there was profuse general urticaria. The urticaria persisted three days and then disappeared.

*CASE 12.—Primary injection, erythema on fifth day, general urticaria on eighth day.*

*Injection of Serum.*—A boy, aged 4, had diphtheria. On July 11, 1907, 12 c.c., and on July 12, 1907, 15 c.c. antidiphtheria serum were administered.

*Reaction.*—On July 16, 1907, there was diffuse erythema over body. On July 19, 1907, there was general mild urticaria. The entire course was afebrile.

*CASE 13.—Primary injection, morbilliform eruption on the eleventh day, with local urticaria.*

*Injection of Serum.*—A boy, aged 6, was given an immunizing dose of 2 c.c. of antidiphtheria serum on June 5, 1908.

*Reaction.*—On June 11, 1908, the patient had no fever. About the site of injection were a few urticarial lesions. Scattered over the body, but most abundant over the forehead, were round or oval papules, looking very much like the eruption of measles in the earlier stages. There were no other signs of measles, no catarrhal symptoms or Koplik spots. No cases of measles developed among fifty-five children exposed.

CASE 14.—*Primary injection, scarlatiniform eruption on ninth day.*

*Injection of Serum.*—A boy, aged 11, had diphtheria. On Aug. 15, 1907, 10 c.c. of antidiphtheria serum were injected.

*Reaction.*—On Aug. 24, 1907, the temperature was 101; the chest, back and abdomen were covered with a rash very closely resembling that of scarlet fever. The following day the temperature was normal and the rash disappeared during the day. No other symptoms of scarlet fever were present. There was no subsequent desquamation.

CASE 15.—*Primary injection, severe general reaction on fifth day with marked involvement of mucous membranes.*

*Injection of Serum.*—Woman, aged 25, had diphtheria. On Oct. 27, 28 and 29, 1906, she was given 22 c.c. of antidiphtheria serum in three doses.

*Reaction.*—Oct. 31, 1906, in the afternoon she complained of pain and distress in the cardiac region. On Nov. 1, 1906, at 8 p. m., the patient had violent urticaria over the entire body; severe pain in gastric region; temperature of 98.6 F.; pulse 92. On Nov. 2, 1906, at 7 a. m., the patient vomited and was very hoarse. Urticaria came and went. On Nov. 4, 1906, she vomited, had normal temperature and slight hoarseness. On Nov. 5, 1906, nausea was present and general severe urticaria. On Nov. 6, 1906, there was quite severe pain in joints and much pain in the gastric region. On Nov. 7, 1906, there was much pain in the joints, but no urticaria. Following this was considerable general depression for two or three days, followed by quite rapid gain of strength.

CASE 16.—*Primary injection, general reaction on eleventh day with involvement of mucous membranes.*

*Injection of Serum.*—A man, aged 22, had diphtheria. From Oct. 19 to 21, 1908, the patient received 100 c.c. of antidiphtheria serum.

*Reaction.*—On Oct. 30, 1908, the temperature had been normal for six days and he had felt generally well. Swelling had almost disappeared from the throat. On Oct. 30, 1908, at 3 p. m., the temperature suddenly rose to 101.6 F., with associated headache. On Oct. 31, 1908, in the morning, the temperature was 101.6 F., and the patient had headache and crampy pains in the epigastrium. The skin of the chest showed a delicate erythema. Some fever continued the two following days. On Nov. 3, 1908, at 4 p. m., the temperature was 103.3, pulse 96, and there was nausea and vomiting. There was headache, general aching in the muscles and extensive severe urticaria. The mucous membranes of the throat and tonsils, previously involved in the diphtheria, were much swollen and sore. On Nov. 4, 1908, in the morning, the urticaria was much less, the temperature 99, and the pulse 84. In the afternoon the patient was very much improved in every way, and from this on the temperature remained normal and no further symptoms of serum reaction returned.

CASE 17.—*Primary injection, general urticarial eruption on tenth day, with return of laryngeal symptoms.*

*Injection of Serum.*—Boy, aged 4, had laryngeal diphtheria. On Dec. 19, 1906, 10 c.c. of antidiphtheria serum, and on Dec. 20, 1906, 30 c.c. of antidiphtheria serum were given in three doses.

*Reaction.*—On Dec. 28, 1906, the boy was convalescent, all laryngeal symptoms having been absent for four days, with normal temperature. On December 29 the temperature was 101 F.; mild general urticaria was present. The patient became quite hoarse. On December 30, 1906, the temperature was 103 F.; there was marked urticaria over the whole body. The patient was very hoarse and croupy. On December 31 the temperature was normal. The patient's hoarseness gone and he made an uneventful recovery.

REACTION FOLLOWING A SECONDARY INJECTION OF SERUM GIVEN AFTER  
AN INTERVAL OF CONSIDERABLE LENGTH. ANAPHYLAXIS

It has been observed by many who have used diphtheria antitoxin on a large scale that when a person receives a secondary injection of serum ten days or more subsequent to the primary one the symptoms of the serum intoxication develop almost immediately or after a shortened incubation period. Cases of this sort were first carefully studied and described by von Pirquet and Schick in 1905 in their valuable monograph on the serum disease, and the following description is largely drawn from that source. According to whether the symptoms appear after a very short interval of a few hours or after a longer interval of three to six days, von Pirquet and Schick have designated such reactions as "immediate" or "accelerated." The immediate reactions may be local or general. In the immediate local reaction or "specific edema," an intense edema appears at the site of injection a few minutes or hours after the secondary injection, reaches its height in twenty-four hours, and gradually subsides in two to five days. The regional lymph glands are often enlarged and sensitive. Slight fever and chilliness are often present. In the immediate general reaction, fever, exanthem and other general symptoms occur within the first twenty-four hours. The urticaria begins almost simultaneously at the site of injection and on the rest of the body and is accompanied by distressing itching. In the face there is apt to be much swelling, especially of the lips and eyelids. The general exanthem is usually urticarial, but may become morbilliform or erythematous. Fever often occurs.

The accelerated reaction follows the secondary infection after an interval of five to seven days. The onset is very precipitate and the symptoms correspond to those observed in the reaction occurring at the normal time after a primary injection—fever, exanthem, edema, joint pains, etc. Individuals who first show an immediate local reaction may, after an interval of four to eight days, show an accelerated reaction, or the accelerated reaction may occur with no preceding local one.

Von Pirquet and Shiek observed 20 children in whom primary and secondary injections were administered with varying intervals. In 6 cases, with intervals of one to six days, no reaction occurred; in 2 cases, with intervals of six and nine months, 1 showed a slight immediate local reaction; in 12 cases, with intervals of three to eight weeks, 11 gave an immediate local reaction and 1 showed a general exanthem on the sixth day. If the interval between the primary and secondary injections is from twelve to forty days, immediate reactions only are to be expected:



if one-half to six months, both the immediate and accelerated reactions may be looked for; if the interval is over six months, accelerated reactions occur in the largest proportion. When the interval is over three months, the immediate reaction is no longer constant, and from this time on it gradually disappears. In one case it was observed after an interval of three years. In their experience, the accelerated reaction first occurred after an interval of twenty-one days, and the longest interval after which they observed it was seven and one-half years. They note that the local reaction follows the administration of smaller quantities of serum, and that it occurs regularly if large doses of serum are employed in the primary injection, and the interval is three to eight weeks.

Following von Pirquet and Schick, several authors have written of cases of a similar nature. Currie, in 1907, recorded 2 cases, one of immediate and one of accelerated reaction out of 5 patients receiving secondary injections after intervals of more than ten days. In a later communication<sup>14</sup> he has reported abnormal\* serum reactions following the use of serum in meningitis. He concluded that the total volume of serum did not affect the frequency of abnormal reactions, and that a preceding normal reaction did not predispose to a subsequent abnormal one. Goodall, in 1907, reported a series of 90 cases in which secondary injections of serum were given after intervals of eight to fifteen hundred and eleven days. Among these, 17 patients (18.8 per cent.) developed an immediate reaction. The shortest interval was thirty-five days and the longest 363 days. He concludes that a secondary injection within five weeks of the primary one is not likely to give rise to an immediate reaction. In 7 of the 17 cases, severe symptoms were presented, in 1 very severe. All the patients recovered. In 1 case rigor was followed by convulsions, in 1 rigor was followed by collapse, in 4 rigor alone occurred, and in 1 case collapse alone. He adds: "Though I have had a very extensive experience of serum treatment, I have never seen an immediate reaction of any kind after a first injection for a primary attack of diphtheria, and I have never seen convulsions, a rigor or vomiting due to serum except as part of such a reaction, with only one, and that a very doubtful, exception."

Of his 90 cases, 30 (33.3 per cent.) showed accelerated reactions. In every case but one the reaction occurred before the fifth day; in 17 on the day following the injection, in 5 on the second, in 2 on the third, in 5 on the fourth and in 1 on the fifth day after the injection. The shortest interval between the primary and secondary injection was eighteen

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14. Currie: Jour. Hyg., 1908, viii, 457.

\*British authors have spoken of serum reactions in persons not previously sensitized as "normal" and in those previously sensitized as "abnormal."

days, the longest was 1,511 days. In 8 cases the accelerated reaction was preceded by an immediate reaction. The accelerated reactions were seldom severe. In 1 case there was collapse and in 1 joint pains. He concludes as follows:

A. When serum reaction occurs at the primary attack (of diphtheria) the patient is more likely to have an abnormal reaction after the second injection.

B. The greater the volume of serum given at the primary attack the more likely is an abnormal reaction to occur after serum at the second attack.

C. An abnormal reaction is most likely to occur after serum in a second attack when a patient has had a large volume of serum followed by a reaction at the first attack.

Umber,<sup>15</sup> in 1908, reported a very severe reaction in a young woman of 22 years. Two years before, she had been treated with serum. The secondary injection consisted of 2.5 c.c. of antidiphtheria serum. Two hours after the injection severe collapse developed, accompanied by marked universal urticaria, great edema of the face, fever, pulse scarcely perceptible and 160 per minute. There was slight enlargement of the area of cardiac dulness. Recovery was complete in ten days. Otto,<sup>16</sup> in the same year, observed a severe reaction in a child following a secondary injection of 0.8 c.c. of serum.

TABLE V.—PATIENTS RECEIVING A SECONDARY DOSE OF SERUM AFTER VARYING INTERVALS

Primary Dose.	Secondary Dose.	Interval.	
12 cc.	16 cc.	15 days	No reaction after either injection.
2 cc.	40 cc.	50 days	Mild general urticaria on 6th day after secondary injection.
32 cc.	140 cc.	3 months	Severe reaction after primary injection. No reaction after secondary injection.
7—	2 cc.	3 months	Local reaction with temperature of 99.8 F., 16 hours after secondary injection.
2 cc.	2 cc.	5 months	No reaction after either injection.
7—	26 cc.	6 months	No reaction after either injection.
7—	4 cc.	8 months	Erythema and urticaria 10 hours after secondary injection.
4 cc.	20 cc.	9 months	No reaction after primary injection. Immediate general urticaria with collapse after secondary injection.
7—	2 cc.	2 years	No reaction after either injection.
7—	4 cc.	2 years	No reaction after primary injection. Severe general urticaria 12 hours after secondary injection.
15 cc.	22 cc.	2 years	No reaction after primary injection. General reaction, 4 days after the 1st, and 1 hour after the second secondary dose. Jaundice.

I have observed 11 cases in which a primary administration of serum was followed by a secondary injection after intervals varying from

15. Umber: *Therap. d. Gegenw.*, 1908, xlix, 480.

16. Otto: *Therap. d. Gegenw.*, 1908, xlix, 498.

eighteen days to two years. A summary of these cases is given in Table 5. It will be noted that no reaction followed the secondary injection in 5 cases, in 1 only of which had a reaction followed the primary injection. As regards the 6 cases in which there was a serum reaction after the secondary injection, in 1 a mild general reaction occurred on the sixth day, in 1 local reaction occurred after sixteen hours, in 2 a general reaction occurred after ten and twelve hours, in 1 there was a very severe immediate general reaction, and in 1 a general reaction occurred four days after the first and one hour after the second secondary dose.

It is noteworthy that no serum reaction occurred after the primary injection in any one of three patients who developed severe reactions after the secondary injection.

Since these cases are of special interest, I have related their histories somewhat in detail (Cases 18 to 23).

#### CASES OF SERUM REACTION FOLLOWING A SECONDARY INJECTION OF SERUM

*CASE 18.—Secondary injection after an interval of fifty days, followed in six days by a mild general urticaria.*

*Injection of Serum.*—A boy, aged 4, had diphtheria. Fifty days previously he was given 2 c.c. of antitoxic serum as a prophylactic measure during a course of scarlet fever. April 5, 1907, he received 32 c.c. and April 7, 1907, 8 c.c. of antidiphtheria serum.

*Reaction.*—April 11, 1907, there appeared a mild general urticaria.

*CASE 19.—Secondary injection after an interval of three months, followed in sixteen hours by a local reaction.*

*Injection of Serum.*—A boy, aged 7, three months before December, 1908, was treated with antitoxin for diphtheria. On Dec. 3, 1908, an immunizing dose of 2 c.c. of antidiphtheria serum was injected.

*Reaction.*—Sixteen hours later there was observed at the site of injection a firm swelling, three inches in diameter, elevated above the surface, with an erythema of the skin over and about the swelling.

*CASE 20.—Secondary injection after an interval of eight months, followed in ten hours by local erythema and general urticaria.*

*Injection of Serum.*—A boy, aged 3, had diphtheria. Eight months before he had received injections of antitoxin for diphtheria. On Jan. 15, 1907, he was given 4 c.c. of antidiphtheria serum.

*Reaction.*—Ten hours after the injection there developed a delicate erythema on the neck and chest, and urticarial lesions over the body. The temperature was not elevated.

*CASE 21.—Secondary injection after an interval of two years, followed in twelve hours by a very severe general reaction.*

*Injection of Serum.*—A woman, aged 23, had received antitoxin for diphtheria in the spring of 1906. No signs of serum reaction followed. On Feb. 27, 1908, she developed a tonsillitis and at 9 p. m. was given 4 c.c. of antidiphtheria serum.

*Reaction.*—Feb. 28, 1908, at 9 a. m., urticarial lesions appeared on the face and arms, but were not very troublesome, and during the following day mild urticaria was present. March 1, 1908, she was so hoarse as to be unable to speak above a whisper. There was a marked coryza, and urticarial lesions were scattered over the body. March 2, 1908, about noon, there appeared a very violent generalized urticaria with great swelling of the lips and eyelids. The hoarseness was less marked. At 4 p. m. the patient complained of choking sensations. The mucous membrane of the pharynx was perceptibly edematous. There was pronounced edema of the hands, wrists and ears. The itching was intense and was associated with great restlessness. A chill occurred at 6 p. m., but the temperature only rose to 99.6 F. At 8 p. m. the patient vomited and fainted on getting out of bed. The pulse was weak, but not very rapid. At 11 p. m. she complained of vertigo. The urticaria was very annoying, and the itching in the soles of the feet was especially complained of. On March 3, 1908, at 2 a. m., the patient complained of nausea, and difficulty in breathing. The pulse was weak; there was no cyanosis; the temperature was 98.6. The patient was unable to sleep; complained of itching in the tongue. At 5 a. m. the eruption had almost disappeared, and the patient felt very weak and depressed. There was no albumin in the urine. During the day the urticaria was mild and troublesome only at times. On March 4, 1908, after midnight the patient slept considerably. During the day she complained much of headache, nausea and vertigo, and of a general feeling of weakness. There was no urticaria. The next day the vertigo had disappeared and the patient felt much improved. For several days she was weak, and only after an additional ten days had she recovered her strength.

*CASE 22.—Secondary injection after an interval of two years, with general reaction four days after the first and one hour after the second secondary dose, and with subsequent jaundice.*

*Injection of Serum.*—A man, aged 22, had diphtheria. Two years previously he had had diphtheria and received 8,000 units of antitoxin. No serum reaction followed this injection. On Nov. 15, 1908, on the appearance of slight soreness of the throat he received 2 c.c. of antidiphtheria serum. The following day there was local itching. On Nov. 19, 1908, at 12:30 a. m., on a diagnosis of diphtheria being made, the patient, immediately after entering the contagious hospital, was given 20 c.c. of antidiphtheria serum.

*Reaction.*—One hour after the injection general urticaria began to appear, and on Nov. 20, 1908, at 8 a. m., a severe general urticaria was present. During the day he was twice given 20 c.c. of antidiphtheria serum. There was slight fever and two attacks of vomiting. On Nov. 21, 1908, in the forenoon, jaundice began to appear. At noon there was very severe urticaria and pronounced edema of face, hands and feet. No albuminuria was present. During the two following days the urticaria was very troublesome and the jaundice became deeper. From that time on urticaria was absent, and the jaundice rapidly cleared up.

*CASE 23.—Secondary injection after an interval of nine months followed by a very severe general reaction in thirty minutes.*

*Injection of Serum.*—A woman, aged 25, on March 1, 1908, was given 4 c.c. of antidiphtheria serum during an attack of tonsillitis. No symptoms of serum reaction followed. During the second week of December, 1908, she suffered from rheumatic pains in the hips and joints of the lower extremities. She had rheumatism several years before. On Dec. 12, 1908, a sore throat with exudation upon the tonsils was diagnosticated by cultures as diphtheria. Dec. 13, 1908, at 7:30 p. m., she was given 20 c.c. of antidiphtheria serum subcutaneously.

*Reaction.*—At 8 p. m. there suddenly appeared a violent urticaria distributed over the entire body, associated with great itching and marked restlessness. At 9 a. m. the patient was in extreme collapse, the skin clammy, the lower ex-

tremities cold, the radial pulse imperceptible, and the patient so nearly unconscious that she could not be aroused. There was no cyanosis or noticeable dyspnea. Under the application of external heat, diffusable stimulants hypodermically and the subcutaneous introduction of large quantities of physiologic salt solution, she gradually emerged from the condition of collapse, and at 10 p. m. consciousness returned, but the radial pulse was still irregular and weak and could not be counted. At 11 p. m. the patient was nauseated and vomited twice. During the few hours the following notes were made on the history:

Dec. 14, 1908, 12:30 a. m., pulse fairly strong; patient drowsy; 2:30 a. m., nausea; 4 a. m., pulse full and regular; temperature, 98.6 F.; 12 m., nausea, headache; 4 p. m., pulse 100, regular and of fair quality, temperature 100.2 F.

Dec. 17, 1908, a. m., urticaria was now very mild.

Patient complained of pain in the legs. From this time on there was gradual improvement, but several days were required for gaining the usual strength.

If this patient had not been situated so as to secure prompt and efficient treatment, one is fearful as to what the outcome might have been.

#### TOXIC EFFECTS OF ALIEN SERUMS IN ANIMALS

Uhlenhuth,<sup>17</sup> in 1897, added much to our previous knowledge regarding the toxic effects of the serum of one animal when injected into others. It was found that the intravenous injection of 7 to 10 c.c. of normal human blood serum, 11 c.c. of sheep serum, 12 c.c. of hog serum and 6 c.c. of cattle serum per 1 kilogram of weight was fatal to rabbits in half an hour. Horse serum did not kill or produce any reaction when injected in quantities as large as 60 c.c. per kilogram of weight in rabbits. The subcutaneous injection in guinea-pigs of 0.5 c.c. of human, rabbit, hog and sheep serum led to local infiltration, and similar injections of 15 to 20 c.c. of the same serums led to local necrosis. H. Pfeiffer<sup>18</sup> confirmed these latter results and showed that the subcutaneous injection of large quantities of horse serum in guinea-pigs caused at most a slight local reaction. The intraperitoneal injection of large quantities—5 to 10 c.c.—of horse serum in guinea-pigs has been found to be entirely harmless by Rosenau and Anderson and many other investigators. Lewis<sup>19</sup> observed slight symptoms of intoxication in guinea-pigs which received 2 c.c. of horse serum into the circulation followed by 5 c.c. intraperitoneally. The effects of the injection of horse serum in man has been already discussed. As a general rule, horse serum is decidedly less toxic for alien species than other serums.

#### ANAPHYLAXIS

In 1904, during Ehrlich's visit to America, his attention was directed by Theobald Smith to the fact, which had often been observed by vari-

17. Uhlenhuth: *Ztschr. f. Hyg.*, 1897, xxvi, 384.

18. Pfeiffer (H.): *Ztschr. f. Hyg.*, 1905, li, 183.

19. Lewis: *Jour. Med. Research*, 1908, x, 608.

ous persons during the testing of antitoxic serums, that guinea-pigs which had received injections of diphtheria toxin and antidiphtheria serum with no apparent effect would become sick or die if a few c.c. of serum were injected after an interval of some weeks. The result was the work of Otto,<sup>20</sup> whose results were published just prior to those of Rosenau and Anderson, who had been trying to solve the same problems. Both investigations, conducted independently, showed that if guinea-pigs were injected with small quantities of horse serum, after a period of ten days they became hypersensitive, so that a second injection of a larger quantity of serum caused alarming and often fatal results. This condition of unusual or exaggerated susceptibility is known as anaphylaxis, hypersusceptibility or supersensitiveness. Guinea-pigs may be sensitized to horse serum by the injection of 0.004 to 0.000001 c.c. of horse serum. An interval of ten to twelve days must pass before the animal exhibits the condition of hypersusceptibility. If a second injection of 0.1 c.c. of horse serum intraperitoneally or of a larger quantity subcutaneously is then administered, the guinea-pig shows certain definite symptoms of intoxication. In five to ten minutes after the injection the animal shows signs of embarrassed respiration, scratches at the mouth, coughs and may exhibit rapid or spasmodic breathing. It soon becomes restless and agitated. This stage is followed by more or less complete paralysis, when the pig lies on the side and the muscles are relaxed. In a short time convulsive movements supervene and death ensues. Death often occurs inside of half an hour and usually within an hour. Some animals survive after passing into the stage of relaxation, and they are then insusceptible to further injections for some time. All of these phenomena have been produced with normal horse serum, and several investigators have conclusively shown that the antitoxin or other immune bodies in the serum have nothing to do with the reaction.

Previous to the time when the experiments just related were carried out, Richet<sup>21</sup> had sensitized dogs with small, non-fatal doses of actinia poison, so that a second dose, also non-fatal in a normal dog, given intravenously after an interval of twenty-one days, produced in a few seconds after injection coughing respiration, great weakness, vomiting, diarrhea, relaxation and death inside of half an hour. The term "anaphylaxis" was introduced by him to designate this condition of hypersensitiveness. Since these pioneer observers published their results, numerous investigations by them and others have yielded most impor-

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20. Otto: *Lenthold Gedenkschrift*, Berlin, 1906.

21. Richet: *Arch. di fisiol.*, 1904, i, 129; *Compt. rend. soc. biol.*, 1905, lviii, 109, 112.

tant results and have shed much light on many phenomena associated with immunity and infection. The major part of this work has been carried out in American laboratories. It has been shown that a primary injection of small amounts of a great number of substances—all of a protein nature—is able to render guinea-pigs hypersusceptible to a subsequent injection of the same substance. Many of these substances are entirely innocuous under ordinary circumstances, and embrace such materials as milk, white of egg, extracts of peas, etc. Wells<sup>22</sup> has shown that egg albumin, freed from the other proteins of egg-white by repeated crystallization, produces typically the anaphylaxis reaction. It sensitizes in doses as small as 0.00000005 gram; fatally in doses of 0.000001 gram. The minimum lethal dose for sensitized pigs is about 0.5 milligram by intraperitoneal injection and about 0.1 to 0.05 milligram when injected into the circulation.

The unpurified mixed proteins of egg-white act in a similar manner, but are less active.

Extracts of various bacteria have been shown also to give rise to the phenomena of hypersusceptibility and anaphylaxis.

By feeding guinea-pigs with uncooked horse flesh and horse serum, Rosenau and Anderson were able to bring about a considerable degree of hypersusceptibility to horse serum. This is of special interest as suggesting a possible manner in which man may be rendered hypersensitive through food, and it may help better to understand those cases of extreme sensitiveness to horse serum on the primary injection. It is also of interest to note that the susceptibility produced by injection of certain protein mixtures is not entirely specific. Rosenau and Anderson pointed out that the injection of the serum of one animal might render the guinea-pig susceptible to other serums, but usually in a less degree than to the one injected. Gay and Southard have shown that, although an animal sensitized by a given proteid will react most violently to a second injection of the same proteid, it will frequently show distinct intoxication on injection of a proteid of different origin. It is reasonable to infer that this would also hold true in cases of sensitization through the alimentary tract.

Any discussion of the exact chemistry of what occurs during the process of sensitization and subsequent intoxication would be largely theoretical. The general opinion seems to be that the sensitizing and toxic substances are identical. Some observations by Gay and Adler<sup>23</sup>

22. Wells: *Jour. Infect. Dis.*, 1908, v, 449.

23. Gay and Adler: *Jour. Med. Research*, 1908, xvii, 433.

seem to indicate that this may not be true. The investigations of Vaughan and Wheeler<sup>24</sup> appear to show that the sensitizing and intoxicating substances are both parts of the same protein molecule, distinct chemically, but each possessing the specific properties of the parent molecule.

The respiratory center in the brain seems to be specifically attacked in the toxic action of the serum in sensitized animals. The heart continues to beat long after respiration has stopped.

It is scarcely necessary to insist on the significance of these investigations as bearing on the serum reactions observed in man. In cases of serum reaction which follow a secondary injection of horse serum, the primary injection having been given several days or longer previously, the analogy with the reaction in guinea-pigs which have been similarly treated is complete. As in guinea-pigs, so in man, this hypersusceptibility lasts a long time. Whether the usual so-called "normal reactions" which are observed to follow a primary injection of horse serum in man are to be explained by assuming a previous sensitization or by the development of a hypersensitiveness after the injection, the serum still remaining in the system after this has developed acting to produce the symptoms of intoxication, is not evident. Instances in which a primary injection of antitoxic serum in man is immediately or very soon followed by death or by symptoms which may be very severe correspond in all essential phenomena with what occurs in sensitized guinea-pigs on the secondary injection. We are ignorant as to the manner in which such individuals are rendered hypersusceptible. Most of them are adults, and many have been subject to asthma. When we remember that the sensitization in experimental animals is not entirely specific, and that it can be produced through foods introduced in the usual manner, we may not be far wrong in assuming that man, being an omnivorous animal, may become hypersensitive through various protein substances taken as food.

Rosenau and Anderson have repeatedly said, "It seems plain that the serums which do not produce untoward symptoms when injected into man are quite as toxic on sensitized guinea-pigs as the serums which have been followed by serious symptoms when injected into man. We believe the difference lies in the susceptibility of the individual and not in the toxicity of the serum." And, again, "We are still unable to account for the ways in which man may be sensitized to a foreign protein. It seems perfectly plain, however, that man may be so sensitized."

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24. Vaughan and Wheeler: *Jour. Infect. Dis.*, 1907, iv, 476.



Since in guinea-pigs the hypersusceptibility is transmitted through the mother to the young, we may infer that this may also occur in man, although we have no data on this point.

It is unsafe to conclude that the phenomena obtained in an animal would be duplicated in another animal or in man under similar conditions. It is known that rabbits react in a different manner from guinea-pigs when treated by injection with horse serum. It is to be expected that in man much variation would be observed as compared to these animals which live a simple life for a comparatively short time, and are fed on quite limited varieties of foods.

#### PROGNOSIS IN SERUM REACTIONS

For some time after the introduction of antitoxin in the treatment of diphtheria there was much active opposition from various sources to its use. Against its use were urged certain fatalities which followed soon after the serum was injected. Many of the objections were founded on unfavorable results following the use of insufficient doses. With the use of larger doses of antitoxin contained in serums of higher antitoxic value, the pronounced beneficial action of the serum in the individual case, and the enormous saving of lives by a reduction of the mortality in diphtheria by 50 per cent. or more, soon quieted all opposition to the use of antitoxin among persons qualified to judge. The tendency now appeared to ascribe all fatalities in individuals who had received injections of antitoxic serums to the disease for which it was administered, and in most instances this position has been shown by subsequent experience to have been correct. With a wide use of antitoxin for immunizing purposes, however, fatal reactions in previously healthy individuals began to be reported from various sources. We now know that fatal results occasionally follow primary injections of horse serum. In persons who have been rendered hypersensitive by injections some time previously, we know that a secondary injection may give rise to violent reactions which in all likelihood may even lead to fatal results in rare instances. Aside from these individuals who have been rendered hypersusceptible by a previous injection of serum or in some manner of which we are still ignorant, there is no fear of a fatal result from the use of serum injections. It is possible that the disturbances associated with the serum reaction in a patient already near the limit of resistance may turn the balance toward the unfavorable side. During the past two years I have been on the watch for such instances, but with one exception, and that not entirely clear, I have not observed a single case. So far as I am able to learn, no case of death has occurred in the diphtheria

wards of Cook County Hospital during the fifteen years since diphtheria antitoxin has been in use which could be ascribed to the serum injected. During this time approximately 3,200 diphtheria patients have been treated, 1,700 having been observed during the last four years. During the past four years immunizing injections of 1,000 units have been given to about 2,000 children with scarlet fever and measles, and in these relatively few serum reactions were observed, and in no case was the reaction sufficiently severe to cause the least apprehension.

If certain precautions which I shall mention later are observed, the danger incident to the use of therapeutic horse serum is reduced to almost an infinitesimal degree.

#### PRECAUTIONS TO BE TAKEN TO AVOID INTOXICATION BY THERAPEUTIC SERUMS IN MAN

A. The required amount of antibodies should be administered in as small a quantity of serum as possible. This will reduce the number and severity of reactions following primary injections.

B. Except in urgent cases, a small quantity of serum (0.5 c.c.) should be injected at the initial dose, waiting a few hours before giving more. This will allow the immediate reaction which sometimes follows a primary injection to develop and the limited amount of serum will reduce its severity. After recovery from this reaction more serum can be given with impunity.

C. In all persons who have had serum previously, and in those in whom this possibility can not be certainly excluded, a small dose of 0.5 c.c. should first be given as indicated above.

D. It is important to give all the serum required in a case as rapidly as possible, so as to avoid injections after hypersensibility has developed.

E. Precautions should be taken to avoid injection directly into the circulation. If a glass syringe is used and gentle traction made on the piston after the insertion of the needle, entrance of blood through the needle would indicate the puncture of a vein and would demand the reinsertion of the needle at another point. It is well known that a given volume of serum injected directly into the circulation is much more toxic than the same quantity injected subcutaneously.

F. Extreme precautions are to be taken in the use of therapeutic serums in persons who have been the subjects of asthma, hay fever, urticarias, etc. In such persons the initial dose should be very small and every means should be at hand to combat immediately any untoward results.

## TREATMENT OF THE PATIENT DURING THE ATTACK OF SERUM REACTION

The administration of calcium salts during the reaction is rational with the purpose of combating the edema. That they have any direct effect in preventing the reaction there is little evidence. In our observation they do not do so. The itching accompanying the urticarias may be much relieved by antipruritic lotions and powders. When there is much swelling of the mucous membranes of the throat, adrenalin solution has given some relief. The extreme restlessness and irritability present in the severe cases may require sedatives. In view of cardiac disturbances sometimes observed during the reaction, with dizziness and faintness on rising, it would seem safer to keep all these patients in bed during the attack. If collapse follows the administration of serum, the treatment follows the direction indicated in conditions of collapse and shock in general. Hypodermic injections of diffusible stimulants, the administration of physiologic salt solution, etc., are to be employed. In the very severe reactions which occasionally almost immediately follow the injection of serum, and in which respiration fails before the heart, artificial respiration is to be resorted to in addition to the other measures.

By placing sensitized guinea-pigs under ether anesthesia before injecting the secondary dose of serum intracerebrally, Besredka<sup>25</sup> prevented the reaction otherwise following the injection, and such pigs were subsequently immune. Rosenau and Anderson<sup>26</sup> were unable to confirm these observations. In cases of asthma in which the administration of serum is very urgent, as in an asthmatic child with diphtheria, it would at least be worth while to consider whether the serum might not best be given after placing the patient under profound ether anesthesia.

THE BEARING OF RARE ACCIDENTS FOLLOWING THE INJECTION OF THERAPEUTIC SERUMS ON THE ATTITUDE OF PRACTITIONERS  
TOWARD THEIR USE

In this connection Lewis has very well said, "In attempting to determine whether a given serum treatment is or is not dangerous, evidently each species of animal must be separately considered. It is almost needless to point out that the data accumulated since 1893 on the accidents incident to the therapeutic use of horse serum, its uncomfortable sequelæ and its great benefits are of much more value as a guide for future practice than conclusions drawn from complex experiments on

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25. Besredka: *Ann. de l'Inst. Pasteur*, 1907, xxi, 957.

26. Rosenau and Anderson: *Bull. 45, Hyg. Lab. U. S. P. H. and M.-H. S.*, Washington, 1908.

the laboratory animals. It would be a most unfortunate presentation of laboratory results on anaphylaxis which should lend itself to even a temporary or slight reaction against a therapy which has so thoroughly justified itself in the case of some diseases and which offers such possibilities for the future in the case of others."

It is impossible to secure comprehensive data bearing on the total fatalities which have followed injections of horse serum. In 1906 Rosenau and Anderson had collected reports of 19 such cases from the literature, and stated that they knew personally of several others which had not been reported. Gillette has recently collected reports of 15 fatal cases, 5 of which had been previously reported. It is likely that there were some of these cases among the ones referred to by Rosenau and Anderson. Of the 15 cases, reports of which were collected by Gillette, 9 occurred in persons with a distinct history of asthma, and in several the antitoxin was administered with the hope that the horse serum would influence the asthma favorably. It would probably be within the bounds of accuracy to estimate that not over 50 cases of death from therapeutic serums had occurred throughout the world in the past fifteen years. When we place by the side of this the fact that many thousands of lives have each year been saved by diphtheria antitoxin alone, the small number of deaths appear insignificant. If we place the reduction in mortality in diphtheria since antitoxin was introduced at the low figure of 50 per cent. during this time in Chicago alone, approximately 160 times as many lives were saved as were lost from the use of serum injections throughout the world. In a single year the lives saved in Cook County Hospital by the use of diphtheria antitoxin, which would otherwise have been sacrificed, may very safely be said to be ten times as great as the total deaths from serums throughout the world in fifteen years. The saving of lives in this one hospital in one month frequently more than counterbalances the entire worldwide loss of life from the use of serum in fifteen years.

With such facts before us, there can be no question that when diphtheria is present it is the duty of the physician to urge the use of antitoxin in every case.

It is only in the prophylactic use of antitoxin that we may raise any question as to limitation of use. Since diphtheria patients treated by means of antitoxin at the beginning of the disease always recover, it is open to question whether persons exposed to diphtheria should be injected with antitoxin for protective purposes only, if they are so situated as to be watched for the early symptoms of the disease. In adults, in whom danger from the serum is greatest, this practice is most question-

able. In the case of children, in whom the danger is the least, and almost *nil*, where they are closely associated in institutions and where they can not be properly watched for early signs of the disease, any slight danger from the serum must be disregarded. The protective dose is also undesirable because it may sensitize the individual to future doses.

In persons to be injected with serum a history of asthma, hay fever, etc., is to be sought, and if such is obtained the patient or parents should be informed of the possible danger in such cases, and no injection of serum should be given without strong indications. The injection of horse serum for its curative effect on asthma is to be discouraged. This has been urged by Dr. Gillette.

The injection of 1 to 3 c.c. of blood serum from a sensitized guinea-pig into a normal guinea-pig renders the latter also hypersusceptible, so that if it is given, after twenty-four to forty-eight hours, an intraperitoneal injection of 5 c.c. of normal horse serum, symptoms of anaphylaxis develop. The blood serum of the sensitized pig is said to contain anaphylaetin which is transferred to the other animal in the injected serum. Rosenau and Anderson have shown that the blood serum of men who have been sensitized by injections of horse serum also contains anaphylactin, which can be demonstrated by the guinea-pig test.

In rare instances this test, as suggested by Otto, may be of value in deciding whether a person can be given horse serum with safety. So far as I am aware no tests of this sort have been made to determine whether the blood serum of asthmatics contain demonstrable anaphylactin.

#### CONCLUSIONS

1. The terms "serum disease" and "serum reaction" are preferable to other expressions which have been used in speaking of the symptoms provoked by injections of alien serums. The reaction is dependent on the proteins of the serum and bears no relation to the antitoxin or other antibodies contained in the serum. In general, the serum of one species of animal is toxic when injected into an animal of another species.

2. The occurrence of a serum reaction after the injection of antiphtheria horse serum is determined in part by the susceptibility of the individual and the toxic properties of the particular serum administered, but in largest measure by the total quantity of serum employed. Precipitated serum calls forth reactions in about the same proportion of cases as does whole serum in corresponding bulk.

3. The interval between the injection and the appearance of the reaction varies from a few minutes to three weeks or more. The major-

ity of reactions appear before the eleventh day. The length of incubation is independent of the number of injections and the quantity of serum.

4. When a primary injection, after an interval of ten days or more, is followed by a secondary one, the subsequent reaction is apt to be intensified and to occur after a shorter incubation period.

5. Serum reactions following secondary injections correspond to the phenomena of anaphylaxis in experimented animals which may be provoked by various serums and also by many other substances of a protein nature.

6. While the administration of antidiphtheria horse serum is usually devoid of danger, in rare instances persons who have been rendered hypersensitive by previous injections or in some hitherto unknown manner may be made alarmingly ill and may even die as the result of such injections.

7. Certain precautions should be observed in the injection of horse serum. Where there is a history of asthma, etc., the possible danger should be distinctly stated before serum is administered. For the protection of other members of the profession who may meet similar experiences, all fatal cases should be reported.

8. The rare occurrence of unfavorable results from the use of antidiphtheria serum should not deter the physician from urging its administration in every case of diphtheria.

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# DISEASES OF THE OPTIC NERVE AS AN EARLY OR EARLIEST SYMPTOM OF MULTIPLE SCLEROSIS\*

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The involvement of the optic nerves in multiple sclerosis is not an infrequent phenomenon. Charcot and Oppenheim consider it even frequent. Uhthoff observed it in at least half of the cases. Kampherstein found it in 70 per cent. Marx<sup>1</sup> found changes in the optic nerve six times in sixteen cases. Consequently changes in the heads of the optic nerves during the course of multiple sclerosis are a well-known occurrence.

Far more important is the occurrence of optic nerve disturbances as an early symptom or as the earliest manifestation of multiple sclerosis. Their recognition is extremely important from a prognostic standpoint. A statistical study of the subject shows that changes of the optic nerve or nerves may precede the onset of other symptoms of insular sclerosis for a period of between ten years and six months. Oppenheim observed one case in which optic neuritis and subsequent atrophy was the only symptom for twenty years. Bruns and Stölting, according to Schley,<sup>2</sup> in twenty cases found it thirteen times as the only symptom.

In the last seven years fifty-six cases of multiple sclerosis have come under my observation in the clinics of various hospitals and in private practice. They all presented the cardinal classical symptoms of the affection. Their number could be augmented, but, as there were cases which, although this diagnosis was probable, nevertheless presented symptoms referable to other organic nervous diseases, I have excluded them from my series. The fifty-six cases presented clinically nystagmus, staccato speech, intention tremor, exaggerated patellar and Achilles tendon reflexes on one or both sides; some of them also presented a history of apoplectiform seizures and vertigo. Twenty-three patients showed changes in the optic nerves. Of these twenty-three I exclude five cases, in which the optic neuritis and atrophy were the earliest or the only sign of the disease; I will discuss them later. Eighteen, therefore, presented changes in the papillæ, together with other symptoms of multiple sclerosis. In how many of these cases the changes in the optic nerves

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1. Arch. f. Augenh., 1907, lix, 28.

2. Berl. klin. Wehnschr., 1908, p. 1724.

developed first, I am unable to say, as they came under my observation when the entire symptom-group was present. A close questioning, however, revealed the fact that some indefinite disturbance of sight in one eye first attracted the attention of eight of these eighteen patients. It is possible that in the eight cases the phenomenon under discussion was the earliest symptom, but, as they came under my care late, I am unable either to confirm or deny the statement. For the sake of accuracy I shall not consider them in my study. In my series, therefore, optic nerve changes occurred in more than 41 per cent. of the cases.

As to the changes themselves, the eighteen cases presented the following at the time of the examination: Optic atrophy was present in eleven cases, in eight of which it was unilateral (on the left), in two more marked in the left eye than in the right and in one bilateral and equal. In the last three the optic atrophy always began on one side, but was rapidly followed by the involvement of the other eye. In the eight cases with unilateral involvement the condition remained confined to the same side for a long time, but finally the other eye became involved. In the remaining seven cases of the series retrobulbar neuritis was present at the beginning for a period of from two to five months and optic atrophy developed later.

Vision in all the eighteen cases was at first very much impaired. Scotomata were present, more on one side than on the other. In the eleven cases with unilateral optic atrophy scotomata were conspicuous on both sides. The central vision was preserved in the majority of the eighteen cases. The acuity of vision was not in direct proportion to the involvement of the optic nerves.

The chief interest of the subject lies in the optic nerve changes as a very early or as the only symptom of multiple sclerosis. I have had five such cases during the last seven years. Three of them I had the good fortune to observe from the beginning and to notice the gradual development of the physical signs of the affection long after the eye symptoms made their appearance. For four years in one case, two and one-half years in the other and six months in the third case optic atrophy remained practically the only symptom, and great hesitation was experienced in forming an opinion as to the prognosis. In the fourth and fifth cases the prognosis is still more difficult, as the other symptoms of multiple sclerosis are practically absent.

Briefly, the histories of the five cases are as follows:

CASE 1.—A man, laborer, aged 39, noticed a gradually increasing dimness of vision in the left eye. At the same time he would have attacks of vertigo. At the end of a month almost complete blindness developed in the same eye. He then came under my observation. An incomplete optic atrophy was found in the



left eye and slight atrophic changes were present in the right eye. The peripheral left visual field was contracted, while the right was preserved. Central scotomata were present in both eyes. For the four subsequent years these were the only signs of the disease and no other symptom pointing to multiple sclerosis could be revealed. At the end of that time the patient contracted pneumonia, from which he made a prompt recovery. Shortly afterward the classical symptoms of insular sclerosis one by one developed.

CASE 2.—A man, aged 34, clerk in a bank, free from a specific or alcoholic history, was taken, without any apparent cause, with a gradually oncoming blindness of the left eye. A month later he also noticed some disturbance of sight in the right eye. An ophthalmoscopic examination revealed partial optic atrophy in both eyes, more in the left than in the right. The vision was almost nil in the left eye and somewhat impaired in the right. The central vision of the right eye was intact and the peripheral visual field was irregularly contracted. Moreover, he presented a dyschromatopsia for the yellow. The external recti of both eyes were in a state of paresis. The condition remained, except for slight variation, practically intact for a period of two and one-half years, at the end of which time the symptoms of multiple sclerosis began to develop. The patient affirms that he accidentally fell off a banister, was stunned, and in about a week a tremor appeared only on voluntary movement. The examination showed a typical picture of multiple sclerosis.

CASE 3.—A man of 31, laborer, free from intoxications and venereal infections, subsequently to a fall from a step-ladder began at the end of six days to complain of poor vision in the left eye. The condition gradually increased and at the end of one month he could see only objects on his left. At the same time he would see spots before his right eye. At the time of examination, two months after the onset, he presented a left retrobulbar neuritis, but no involvement of the optic nerve on the right. The vision was very poor on the left and objects could be perceived with the left eye only when placed externally; the rest of the left visual field was blind. In the right there were several scotomata irregularly distributed. Not a single physical sign of an organic disease of the nervous system was discoverable. The condition remained unchanged for the following month, signs of a progressive optic atrophy were found in the left eye and a retrobulbar neuritis in the right eye. Two months later a complete left and incomplete right optic atrophy, with increasing failure of vision in the right eye, were noticed. At the same time the patient began to have attacks of vertigo. Six months after the onset of the eye disturbances appeared nystagmus, scanning speech and intention tremor; also increased patellar tendon reflexes. The picture of multiple sclerosis was complete.

CASE 4.—*History*.—A man of 28, bookkeeper by occupation, noticed about three and one-half years ago a gradually oncoming drooping of the left upper eyelid, double vision, difficulty in discriminating letters, peculiar dryness of the left eyeball, and weakened vision in the left eye, which kept on increasing until almost complete blindness ensued five months later. At the same time there were dizziness and headache; the latter was confined to the left side of the head. About three months later weakness of vision developed in the right eye, which was also progressive, but did not terminate in marked blindness. The condition remained unchanged until late in November, 1908. During that interval there was no return of headache or dizziness. At this time the patient began to suffer from paroxysmal attacks of vertigo, also from attacks of unconsciousness. He was picked up on the street on several occasions and taken to various hospitals. His memory became impaired and at times he would become confused for a day or two.

*Examination.*—This shows inability to see with either eye on the temporal sides; on the nasal sides there are a few scotomata in both eyes. He therefore has a bitemporal hemianopsia. The pupils react to light and accommodation. Test for Wernicke's pupil in both eyes is negative. The eyegrounds show a very marked optic atrophy on the left and less marked on the right. The left upper eyelid droops only at times. Nystagmus is absent. The examination for other physical signs is negative, except perhaps a slight ataxia of the upper extremities. There is no disturbance of speech, no intention tremor, no changes in the reflexes, no involvement of sphincters.

*Diagnosis.*—In making a diagnosis, cerebral neoplasm, cerebral syphilis, tabes, multiple sclerosis and chronic intoxication have been considered. The absence of vomiting and headache for almost three years, the apparently unaltered condition of the eyes, the absence of localizing signs—all these are against a neoplasm. Cerebral syphilis, I believe also, can not be accepted in view of the absence of headache, of disappearing and reappearing symptoms, and of mental disturbances for three whole years. The normal patellar tendon and Achilles tendon reflexes, the absence of sphincter disturbances, of sensory disturbances, of ataxia, of Argyll-Robertson pupil—all these factors militate against the diagnosis of tabes. Intoxications with alcohol and tobacco, lead, arsenic and carbon monoxide may give place to an optic neuritis with subsequent atrophy, also to contraction of the visual fields; but the eyeground changes are usually bilateral from the very beginning. Besides, the history shows that the patient was not subject to any of these intoxications. He would only occasionally drink a glass of beer and smoked cigarettes very moderately. Moreover, the blindness came many months before he began to use beer. For the reason of the gradual and successive invasion of the eyes and unconsciousness from which he suffers now, I believe the patient is in the early stage of multiple sclerosis.

*CASE 5.—History.*—A young man of 32, salesman by occupation, noticed about seven years ago that his vision began to fail in one eye and only a few months later in the other. A careful investigation shows that he had at that time a double optic neuritis, more marked on one side than on the other. The disturbed vision gradually increased, but during the last two or three years it remained practically unaltered.

*Examination.*—At present (January, 1909) the vision is fair only for outlines of objects, but details can not be distinguished by the patient. The eyegrounds, according to Dr. Oliver, who has kindly referred the case to me, show double optic atrophy. The pupils react to light, but not very promptly. The ocular muscles functionate normally. During six years the patient has not presented any other disturbance; he has been in perfect health. Apart from the eyes there are only two physical symptoms to which attention may be called, exaggerated patellar tendon reflexes, and a slight intention tremor of the left hand. How long these two symptoms have been in existence I am unable to say, as it is only very recently that the patient came first under my observation.

*Diagnosis.*—At all events, if the case is one of multiple sclerosis—and I believe it is—the eye ground changes are the most conspicuous, and there are only two other physical signs of the disease, which, however, are very slight. It is therefore again with a very early or earliest involvement of the optic nerves that we are dealing here. The only obstacle, from a diagnostic standpoint, is the history of a slight erosion on the penis nine years ago, coincident with gonorrhea. Whether the erosion was specific or not, it is impossible to say; but the man never had any other evidence of syphilitic infection and during seven years has not suffered from headache or from sphincter disturbances or any other disorder that we are accustomed to meet in cerebrospinal syphilis. His health has been perfect. The patient has always been free from intoxications and infections of any nature. By exclusion, the diagnosis of multiple sclerosis becomes inevitable.

The five cases just related are almost identical as to their eye symptoms. In the first three the involvement of the optic nerves with disturbance of vision appeared first, and many months later the classical symptoms of multiple sclerosis began to develop. In the fourth case, if it is one of multiple sclerosis, the eye symptoms are the only sign of the disease. Three and one-half years have elapsed since visual disturbances made their first appearance. So far the islets of sclerosis are confined to the cerebrum. In Oppenheim's case the eye symptoms existed twenty years before the typical symptoms of multiple sclerosis entered the scene. In the fifth case, in addition to the optic atrophy which had been in existence seven years, there are only two physical symptoms of multiple sclerosis.

The question of prognosis in cases with early evidences of optic nerve involvement is of paramount importance, especially when the eye symptoms alone are present. A careful and minute examination for physical signs, a close investigation as to intoxications, and a carefully conducted differential diagnosis will determine the prognosis. The simultaneous or early bilaterality of changes in the eye grounds are in favor of intoxications, while unilaterality or successive invasion, particularly at a more or less long interval, are in favor of multiple sclerosis. Scotomata or contraction of visual fields are not a different criterion, as they may be encountered in many conditions. A concentric contraction of the visual fields, frequent in hysteria, is, however, very rare in multiple sclerosis. Bitemporal hemianopsia (in the fourth case) is a rare occurrence in multiple sclerosis.

Cases of multiple sclerosis with symptoms of intracranial pressure have been observed and verified at autopsy, but these symptoms are by far less conspicuous in this affection than in cerebral neoplasms. Ophthalmoscopically the following changes are observed, according to Uhthoff. Either the papillæ are completely atrophied and discolored or the discoloration is incomplete and the most external portions are the most discolored; instead of atrophy there may be an optic neuritis with hyperemia and dilated vessels.

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## ANAPHYLAXIS\*

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Anaphylaxis (*ana*, against, and *phylax*, guard, or *phylaxis*, protection), also called hypersusceptibility, supersensitiveness, is a condition of unusual or exaggerated susceptibility of the organism to foreign substances. The word "anaphylaxis" was introduced by Richet to describe a contrary condition to prophylaxis. As we now regard the phenomenon, the word is a misnomer, for we look upon the condition of hypersusceptibility as a distinct benefit and advantage to the organism. In fact, protection against a large class of infections depends on an altered power of reaction, *i. e.*, hypersusceptibility or anaphylaxis.

This state may be congenital or acquired, and is specific in nature. The condition of anaphylaxis may be brought about by the introduction of any strange protein into the body. Hypersusceptibility to proteins that are non-poisonous in themselves may readily be induced in certain animals.

An animal may be in a condition of hypersusceptibility and immunity at the same time. The two conditions are closely interwoven; the latter is often dependent on the former. Von Pirquet advises that the term "immunity" be limited to indicate the condition of complete resistance in which no clinical reaction occurs, when poisons such as diphtheria, tetanus, etc., are introduced into the organism. He suggests the term "allergic" to indicate conditions of acquired immunity associated with anaphylaxis.

In the case of vaccinia the reaction to a primary "take" appears after an incubation period of four days. In a secondary vaccination the period of incubation is shortened and the clinical reaction lessened. In other words, the power of the organism to react has changed. This increased power of immediate reaction protects the individual. There is no absolute immunity in this class of diseases; the prophylaxis depends on the anaphylaxis.

Allergic then, as the word indicates (*allos* change, and *ergon* action), is an altered power of the organism to react. When this power of reaction is increased we say that the body is hypersensitive or in a state of anaphylaxis.

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The tuberculin and mallein reactions are well-known instances of anaphylaxis. These substances are not poisonous when introduced into a healthy individual, but the tuberculous individual is anaphylactic to tuberculin, and an individual suffering with glanders is in a state of hypersusceptibility to mallein.

A clinical instance of anaphylaxis is the hypersusceptibility of some individuals to pollen—hay fever. The best studied instance of experimental anaphylaxis is that produced in the guinea-pig by the injection of a foreign protein; for example, horse serum, egg-white, milk, etc. Especial study has been made of the anaphylactic action of the blood serum of the horse, partly because that serum is so much used in serum therapy.

It has long been known that the blood of certain animals is poisonous when transfused or injected into certain other species. Many instances might be cited showing that the blood serum of an animal of one species has poisonous properties when injected into an animal of another species. But the blood serum of the horse apparently lacks such poisonous action. Very large quantities of the blood serum of the horse may be injected into man, rabbits, guinea-pigs, and many other animals without serious inconvenience except occasionally a slight reaction at the site of inoculation.

In a certain proportion of cases the injection of horse serum into man is followed by urticarial eruptions, joint pains, fever, swelling of the lymph nodes, edema, and albuminuria. This reaction, which appears after an incubation period of eight to thirteen days, has been termed by Von Pirquet and Schick the "serum disease."

In exceptional cases, sudden death has followed an injection of horse serum in man.

We have shown that ordinarily horse serum is a comparatively bland and harmless substance when injected into certain animals; but these animals may be rendered so susceptible that an injection of horse serum may produce death or severe symptoms. For example, large quantities of horse serum may be injected subcutaneously, into the peritoneal cavity, into the brain, or directly into the circulation of a guinea-pig without apparently causing the animal the least inconvenience. If, however, a guinea-pig be injected with a small quantity, say 0.004 c.c., of horse serum and, after the expiration of a certain interval, again injected with horse serum the result will probably be fatal. The first injection of horse serum has sensitized the animal in such a way as to render it very susceptible to a second injection of horse serum.

A certain time must elapse between the first and the second injections before the animal becomes susceptible to a second injection. This period of incubation is from seven to twelve days, and corresponds suggestively with the period of incubation of the serum disease, which von Pirquet and Schiek place at eight to thirteen days.

Guinea-pigs may be sensitized with exceedingly small quantities of horse serum. In most of our work we used quantities less than 0.004 c.c., and we found in one instance that 0.000.001 c.c. of horse serum was sufficient to render a guinea-pig susceptible.

Wells has recently shown that guinea-pigs may be sensitized with 0.000,000.05 of a gram of egg albumin freed from the other proteins of egg-white.

It also requires very small quantities of horse serum, when given in a second injection, to produce poisonous symptoms. One-tenth of a cubic centimeter injected into the peritoneal cavity is sometimes sufficient to cause death; 0.1 c.c. subcutaneously may cause symptoms, while much smaller amounts given into the brain or directly into the circulation may be fatal.

At first we thought that diphtheria antitoxin had some relation to this phenomenon; we are now able to state positively that it has nothing whatever to do with the poisonous effects of horse serum; further, that diphtheria antitoxin in itself is absolutely harmless. The toxic action which we have studied is caused by a protein in normal horse serum and is entirely independent of the antitoxic properties of the serum.

#### REVIEW OF LITERATURE

Early in the last century Magendie<sup>92</sup> found that rabbits which had tolerated two intravenous injections of egg albumin without any ill effects immediately succumbed to a further injection made after a number of days. Later, workers with preeipitins have frequently found that some of their animals died suddenly during the course of treatment from no apparent cause, while what really happened was that they were in a state of anaphylaxis to the foreign proteid. Other analogous instances may be found scattered throughout the early literature.

In 1888 Arloing<sup>7</sup> expressed the opinion that pathogenic micro-organisms secrete soluble substances which influence the organism in such a way that at a later infection they succumb more quickly. The organism is robbed of its natural protecting bodies through the first process. Arloing evidently had in mind that the power of reaction of an organism could be changed.

In 1891 Courmont<sup>36</sup> studied this question with reference to the tubercle bacillus and the subject was further pursued by the Lyons School with staphylococci, streptococci, *B. pyocyaneus*, and other bacteria.

Brieger,<sup>30</sup> in 1895, immunized a goat to a high degree against tetanus. The blood and milk of this animal contained large quantities of antitoxin. The animal, however, died of tetanus.

Knorr,<sup>82</sup> in 1895, studied this unexpected phenomenon more closely and found that guinea-pigs developed an increasing sensitiveness to tetanus toxin after repeated sublethal doses.

Uhlenhuth,<sup>148</sup> in 1897, worked on the relative toxicity of blood serum in health and disease. He found that intravenous injection into rabbits was not reliable and therefore used subcutaneous injections into guinea-pigs. He found that the normal sterile blood serum of man, sheep, hog, rabbit and cattle even in small doses (about 0.5 c.c.) produced infiltration in guinea-pigs when injected subcutaneously and necroses when given in large quantities. Twenty c.c. of these serums (10 to 15 of cattle serum) is sufficient to cause the death of guinea-pigs. Normal horse serum is not toxic, even in large doses (20 c.c.); at most it only produces slight infiltrations which are rapidly absorbed.

Hericourt and Richet,<sup>77</sup> in 1898, in studying the effects of eel serum on dogs, found that they were not able to immunize them against the serum, but that on the contrary there was an increasing sensibility to it, so that finally the dogs died.

Courmont,<sup>37</sup> in 1900, found that a guinea-pig might support an intraperitoneal injection of a pleuritic effusion of about one-fifteenth its weight (30 c.c. for a 400-gram guinea-pig), without fatal effect, whereas doses very much smaller (several c.c.) given in repeated injections under the skin or into the peritoneum caused edema and death.

Von Behring and Kitashima,<sup>153</sup> in 1901, repeating some of Knorr's work, found a similar instance in a horse immunized against diphtheria. This curious phenomenon, sometimes seen with bacterial toxins, was called hypersusceptibility and was spoken of as a paradoxical reaction. Von Behring and Kitashima then made their experiments on guinea-pigs. Von Behring looked on the hypersusceptibility as purely histogenetic.

Portier and Richet,<sup>109</sup> in 1902, found that if dogs were given a very small dose of a glycerin extract from the tentacles of actinia, and then in fifteen or twenty days given a second small dose, the animals quickly succumbed. The dose given was so small as to cause no symptoms in a normal animal. They proposed the word "anaphylaxis" to indicate hypersensitiveness to a poison.

Arthus,<sup>9</sup> in 1903, studied the effect of repeated injections of horse serum on rabbits and found that if a rabbit were given repeated injections of horse serum at some days' interval it caused, even in small doses, results which, according to the number of the previous injections and methods of injection, were local or general, benign or grave.

Von Pirquet,<sup>167</sup> in the end of 1902, noticed that the symptoms following a second injection of horse serum in a child occurred on the same day and concluded therefrom that the current views on the period of incubation must be wrong. He believed that the organism must be changed through the production of antibodies and that the incubation period was the terminus of the production of these antibodies.

Von Pirquet and Schick,<sup>167-168</sup> in 1903, stated that an organism treated with a foreign serum was distinctly changed from one that had not been so treated. They believed that the strange serum did not work directly on the organism, but that there must be a reaction product or antibody. At the second injection the reaction might occur at once. This they called the "immediate" reaction. When the period of incubation was shortened they called it "accelerated" reaction. Von Pirquet and Schick found a number of analogies between these phenomena and the incubation periods of certain diseases, and mention specifically vaccination and the tuberculin reaction. Hypersusceptibility was shown in the case of injection with horse serum as well as tuberculin in those sensitized with tuberculosis.

#### 1904

Wolff-Eisner,<sup>170</sup> toward the end of 1904, worked on the question of hypersusceptibility in the sense of Pfeiffer's endotoxins. From this starting point he handled the subject broadly and published his views. He studied the lysis of pigeon's blood corpuscles and human spermatozoa after the first and second injections into the peritoneal cavity of a guinea-pig. He observed that guinea-pigs always succumbed at subsequent injections. He explained this phenomenon on the ground that poisonous substances or endotoxins contained within the cells are freed when the cell membrane is dissolved. This solution is produced through a lysin formed by the previous treatment.

Detre-Deutsch,<sup>43</sup> in 1904, studied the question why persons with syphilis do not show, on secondary inoculation, a primary lesion. He carried out experiments on guinea-pigs by reinfecting them with tuberculosis and showed the difference between the course of the first and the second injection, which he called "superinfection." His explana-



tion of the acute action of the second injection coincides with Koch's addition theory of the tuberculin reaction.

1905

Richet,<sup>117</sup> in studying two poisons (congestine and thalassin) extracted from actinia, found that if a very small dose, which caused practically no symptoms in a dog, was followed after twenty-two days by another small dose the animal became very sick or quickly died. He found that not only did his animals remain anaphylactic for a long time, but that it was necessary that a certain time elapse between the first and the second injections for the development of this increased susceptibility to the foreign protein. He further states that anaphylaxis is a new phenomenon which has never before been named or described, and that it is of the same order as that produced by the injection of tuberculin in an animal suffering from tuberculosis.

Von Pirquet and Schick,<sup>170</sup> in a monograph on the serum disease, describe in detail this syndrome which sometimes follows injections of horse serum in man. They show that the symptoms of this disease when caused by a second injection may either appear at once (the immediate reaction) or after a shortened period of incubation (the accelerated reaction). From these clinical observations von Pirquet and Schick draw original and far-reaching conclusions. They show the relation of these clinical observations to the phenomenon of hypersusceptibility, and indicate the importance of these facts in general pathology. They draw attention to the analogy to the tuberculin reaction as a well-known instance of hypersusceptibility. Von Pirquet and Schick believe that the serum reactions give a possible explanation of the period of incubation of infectious diseases and finally conclude that the immunity caused by vaccine and a group of infections is due to the power of immediate reaction acquired by the organism.

During Ehrlich's visit to America in 1904, Theobald Smith told him that guinea-pigs which had been used in testing the potency of diphtheria antitoxin became acutely sick or died from a subcutaneous injection several weeks later of several cubic centimeters of normal horse serum. Ehrlich gave the problem to Otto<sup>104</sup>, who worked out many essential features of the phenomenon, to which he gave the name of the "Theobald Smith phenomenon."

Otto showed what is now well known to be the result of a second injection of horse serum into guinea-pigs. He demonstrated that the diphtheria poisons played no part in the phenomenon. He found, however, that guinea-pigs first treated with mixtures of diphtheria toxin

and serum were more susceptible than those treated with serum alone. Otto showed further that immunity to the poisonous action of the serum injection might be acquired by repeated injections of large amounts of serum at short intervals. He demonstrates that this hypersusceptibility bears no relation to the specific precipitins. Finally, he discusses the relation of the Theobald Smith phenomenon to the cases of reinjection in man and cites instances of alarming symptoms following the second injection of antitoxic horse serum.

Pfeiffer<sup>108</sup> confirmed Uhlenhuth's observations that certain sera, for example hog and sheep serum, caused gangrene of the skin and subcutaneous tissue when injected into a guinea-pig. On the other hand, the serum of horses and rabbits caused practically no reaction. Pfeiffer demonstrates that through repeated injections of normal serum it is possible to immunize the animals against this necrotic action and also that the serum of immunized animals is able to protect animals of the same species. He further confirms Uhlenhuth's explanation of the phenomenon by assuming that the serums contain a haptin in the sense of Ehrlich's side-chain theory. He believes the necrotic action to depend on and to be identical with hemolysis.

#### 1906

Rosenau and Anderson give the results of their studies, with special relation to anaphylaxis in guinea-pigs. They show that a single injection of horse serum is harmless for normal animals. Horse serum is, however, poisonous to a guinea-pig which has previously been injected with horse serum. The period of incubation was determined to be about ten days. The poisonous principle appears to act on the respiratory centers. The heart continues to beat after respiration ceases. It is shown that the toxic action of horse serum bears no relation to diphtheria. The poison is not toxin. Diphtheria antitoxin plays no part in this poisonous action and in itself is harmless. The effects of chemical, physical and electrical influences on the toxic and sensitizing principle are considered. It is shown that guinea-pigs remain susceptible a very long time and that very small quantities (in one instance 0.000,001 c.c.) of horse serum are sufficient to render guinea-pigs susceptible.

It is shown that an active immunity against the toxic action of horse serum may readily be established by repeated injections of horse serum at short intervals into a guinea-pig. Rosenau and Anderson did not succeed in transferring this immunity in the blood serum or body juices to another guinea-pig. It therefore appears that the immune

body, if one exist, against the toxic action of horse serum is not free in the blood or body juices.

It is shown experimentally that the guinea-pig may be sensitized by feeding with horse serum or with horse meat,

It is further shown that susceptibility to the toxic action of horse serum is transmitted from the mother guinea-pig to her young.

The specific nature of the phenomenon is shown. The opinion is expressed that the substance which sensitizes the animal is identical with that which later poisons it. The substance must, however, first cause a reaction in the organism, resulting in the production of antibodies. How man may be sensitized is considered in relation to the cases of collapse and sudden death following the injection of horse serum.

Anderson,<sup>2,3,4</sup> found that female guinea-pigs could transmit to the same offspring hypersusceptibility to horse serum and immunity to diphtheria toxin. This fact, Anderson states, is of great importance in testing antitoxic serums and necessitates care in the selection of breeders for guinea-pigs to be used in serum work.

Vaughan<sup>150</sup> advanced the theory that the first injection of the strange proteid is broken up into components, one of which is toxic, but that the animal is not poisoned because this breaking up takes place slowly. The cells, however, learn from this lesson how to break up the complex molecule, so that when more of the strange proteid is introduced at the second injection it is violently rent asunder, quickly liberating large quantities of the toxic principle of the complex molecule.

McClintock and King,<sup>96</sup> as a result of their work, conclude that the sensitizing action of horse serum given by the mouth is not nearly so great as when given subcutaneously or intraperitoneally.

Remlinger<sup>113</sup> found, in experiments on dogs, rabbits and guinea-pigs, an entire absence of anaphylaxis.

In his first series of experiments, he gave his animals normal horse or sheep serum or antidiphtheric or antitetanic serum; one month later, they received from 5 to 20 c.c. of a mixture of equal parts of antirabic sheep serum and emulsion of fixed virus.

In the second series of experiments, the animals were first treated with a mixture of fixed virus and antirabic sheep serum, and six or eight weeks later were given the serums above mentioned. None of the animals in either series showed any immediate symptoms, though two guinea-pigs and four rabbits died in five or six days.

These results, so contrary to all of the anaphylactic work, may be concerned, in part, with the question of specificity.

Von Pirquet<sup>157</sup> explains the theoretical considerations of the accelerated reactions with special reference to vaccinia. The different characters of the areolas and the papular reactions are described and the conclusion drawn that vaccination does not cause an absolute immunity, but changes the power of reaction of the organism in such a way that it reacts sooner. Thus, when the organism is reinfected the process comes to a conclusion in a short time.

In a brief note von Pirquet<sup>158</sup> suggests the name "allergie" (*allos* change, and *ergon* reaction) to indicate that condition of immunity achieved through an altered power of reaction. The close association between immunity and hypersusceptibility and the relation of these processes to the so-called endotoxins is discussed. Von Pirquet advises that the term "active immunity" should be limited to those conditions in which the introduction of a foreign substance into the organism causes no clinical reaction, that is, in which there is a complete lack of susceptibility. He discusses whether this is produced through alexins (natural immunity), through antitoxins (active or passive immunity against diphtheria and tetanus), or whether it is caused through a form of adaptation. (Wassermann and Citron.)

Von Pirquet<sup>159</sup> concludes that the accelerated reaction in vaccinia is a specific reaction between the virus of cowpox and an immune or allergic organism. The accelerated reaction depends quantitatively upon the amount of the virus that is introduced. From the theoretical standpoint von Pirquet expresses the belief that the accelerated reaction is caused by the coming together of the vaccine virus with the antibodies in the allergic organism and that the precipitins are not concerned.

1907

Gay and Southard<sup>56</sup> found in guinea-pigs dying from the second injection of serum and in those which had severe symptoms and were later chloroformed, what they considered characteristic lesions. Considerable hemorrhages, rather definitely localized, are the characteristic gross lesion. The hemorrhages may be in one or several organs, gastric hemorrhages being especially frequent. Microscopically, there are in addition to the naked-eye hemorrhages, minute, interstitial and oozing hemorrhages. They also claimed to have found fatty changes in voluntary muscle fiber, heart muscle fibers, and in nerve fibers.

Their explanation of serum anaphylaxis in the guinea-pig is substantially as follows: There is a substance in horse serum (anaphy-

lactin) which is not absorbed by the guinea-pig tissue, is not neutralized, and is eliminated with great slowness from the body. When a guinea-pig is injected with a small amount of horse serum the greater part of its elements are quickly eliminated; the anaphylactin remains and acts as a constant irritant to the body cells, so that their activity for the other elements of horse serum is greatly increased. At the end of two weeks of constant stimulation by the anaphylactin a condition is arrived at in which, if the cells are suddenly presented with a large amount of horse serum they are overwhelmed in the exercise of their increased assimilating functions, and functional equilibrium is so disturbed that local or general death may occur.

In a second paper Otto<sup>105</sup> demonstrated that guinea-pigs might be sensitized by injecting them with the blood serum of sensitized guinea-pigs, and further brought out the important point that guinea-pigs sensitized by such a transfer reacted within twenty-four hours. He believes that the first injection results in a weakening or depressing of the portions ("rests") of the antigens which are in the body and thus an apparent hypersusceptibility results. The duration of this hypersusceptibility depends on the amount of serum injected the first time.

Besredka and Steinhardt<sup>22</sup> studied with much care certain features of hypersusceptibility to horse serum in guinea-pigs; they note that the French serums are much less toxic than those used by Otto in Frankfurt and the serums used by Rosenau and Anderson. Besredka and Steinhardt had a mortality of about 25 per cent. when 5 e.c. of serum were given intraperitoneally at the second injection, whereas death was the rule in our experiments under similar conditions. Most of their work was done with doses of 0.05 to 0.25 e.c., given directly into the brain, which either killed or caused grave symptoms in susceptible guinea-pigs. Besredka and Steinhardt lay stress on the production of "antianaphylaxis," which we termed "immunity." They found that a single injection of serum, given into the peritoneum of a sensitized guinea-pig, quickly conferred immunity to a subsequent injection of 0.25 e.c. into the brain; in one case the antianaphylaxis was present one and a half hours after the injection into the abdominal cavity. They were unable to demonstrate any protective properties in various organs of immune guinea-pigs.

Besredka and Steinhardt<sup>23</sup> found that guinea-pigs could be put in a state of antianaphylaxis by the injection of horse serum into the brain as well as into the peritoneal cavity. They consider it a phenomenon of the same order as the disintoxication *in vitro* of the tet-

anized brain by antitetanic serum. They found that guinea-pigs could not be sensitized by intracerebral injection.

They think that their results seem to indicate that the phenomena of anaphylaxis and antianaphylaxis are similar to the precipitating and absorbing actions which govern the relation of colloids among themselves.

Besredka<sup>15</sup> concludes that the toxicity of therapeutic serums may be measured by means of intracerebral injections into sensitized guinea-pigs. Measured in this way, different serums show a wide range of toxicity, the fatal dose varying from 1/4 to 1/128 c.c. This toxicity resides in the serum and not in the cellular elements.

The serums of horses living under apparently the same conditions have about the same toxicity; individual variations are rare and of little importance. The difference in the toxicity of serums appears to be due, in the first place, to their origin; and, in the second place, to their age. Serums are hypertoxic on the day of bleeding, and gradually lose their toxicity. This loss, rapid at first, becomes gradual after the tenth day. All therapeutic serums should be considered toxic within two months of bleeding. In a general way, all serums that excite grave anaphylactic phenomena in doses of 0.0625 to 0.05 c.c., and *a fortiori*, above this amount, should be considered toxic.

Besredka finally states that the technic and dosage by the intracerebral method is rapid, simple, and not expensive.

Besredka,<sup>16</sup> in a preliminary note, states that serum heated to 100 C. has lost all of its toxicity for sensitive guinea-pigs, but still possesses some vaccinating properties: while serum heated to even 120 C. is still sensitizing. He believes there are two substances in horse serum: (a) the *sensibilisinogène*, which is thermostabile and gives birth to the *sensibilisine*, which creates the anaphylactic state; (b) the *antisensibilisine*, which is thermolabile and, being an antibody, combines with the *sensibilisine* when the two come in contact. It is the sudden union of these two at the nucleus of the nerve cell which causes the symptoms of anaphylaxis, especially marked when the second injection is given into the brain.

Besredka<sup>16</sup> considers that there may be two ways in which the toxic property of serum for sensitive guinea-pigs can be altered. These are *directly* on the serum, and *indirectly* on the animal itself. Of all the various *direct* means, such as chemical, physical or biological, only heating the serum to high temperature is of avail. The toxic property is progressively decreased by heating from 76°C. until at 100°C. it disappears. He also finds that the immunizing power of the heated serum follows

the same curve as the toxic property. The repeated heating of the serum three or four times at lower temperatures, such as 50°C. or 60°C. diminishes the toxic property three or four times.

As *indirect* means, he cites the use of serum as a preventive measure, either during the preanaphylactic period or after the period of incubation. He states that ether narcosis prevents the appearance of anaphylactic symptoms, but that neither morphin nor extract of opium has any influence on the appearance of the symptoms.

In a further contribution to the subject Rosenau and Anderson<sup>130,131</sup> studied particularly the relation of anaphylaxis to immunity. They express the opinion that profound chemical changes, perhaps in the central nervous system, are probably produced by the first injection of a strange protein. Many details concerning the sensitizing and toxic principle were studied. In addition to extending and confirming their work on the specific nature of the phenomenon they made further observations on the relation of various physical influences and chemical substances on the reaction. Among other things they brought out the fact that proteids extracted from the bacterial cells and injected into guinea-pigs produced, on the second injection, the same train of symptoms as in the case of serum anaphylaxis. It was found that in certain instances the hypersusceptibility manifesting itself from injections of these bacterial extracts left the animal immune to the corresponding infection.

Rosenau and Anderson<sup>132</sup> later demonstrated the specific nature of anaphylaxis by showing that guinea-pigs may be in a condition of anaphylaxis to three protein substances at the same time. For instance, a guinea-pig may be sensitized with egg-white, milk, and horse serum and subsequently react in a brief period of time to a second injection of each one of these substances. It may be sensitized by giving these strange proteins either at the same or at different times, in the same or in different places, or by injecting them separately or mixed. The guinea-pig differentiates each anaphylactic-producing protein in a perfectly distinct and separate manner. The animal acts as though susceptible to three separate infectious diseases. The conclusion is therefore drawn that the phenomenon of anaphylaxis is specific and the belief expressed that the work indicates that chemical changes rather than morphologic alterations lie at the basis of this phenomenon.

Von Pirquet<sup>162</sup> again clearly defines his conception of *allergie* and points out that a complete immunity does not exist. For example, in revaccination there is an immediate though slight clinical reaction and it is on this condition of hypersusceptibility that immunity depends.

The convenience and advantages of the cutaneous vaccination for studying the problem and for diagnosis, especially in tuberculosis and other infectious diseases, are discussed.

Von Pirquet's<sup>103</sup> admirable clinical studies on vaccination and vaccinal allergic are fully described by him in a brochure published in 1907. The clinical side of primary vaccinations are first considered and then the clinical side of secondary vaccinations are pictured and discussed. He gives a clear picture of accelerated reaction in all its details largely by the use of curves and tables. Finally, von Pirquet's conception of allergic in relation to the early vaccinal reactions is explained. The theories of hypersusceptibility are fully discussed and their relation to the phenomenon of vaccination are considered. Von Pirquet concludes in part that these vaccinal characteristics were more or less known by the old vaccination physicians but, up to now, have been forgotten.

The new points discovered by von Pirquet are especially the morphological, the early reaction and the method of presenting them in curves. The observation that the normal time of reaction is gradually changed to the "immediate" reaction in secondary vaccinations is also new. Von Pirquet further brings forward his conception of the cachectic reaction and the differentiation between the papular and the areolar reactions. He insists on the presence of antibodies which lie at the foundation of accelerated reaction. An analysis of the local symptoms is divided into two processes: one, the growth of the infective principle; and second, the production of antibodies in the organism which explains the accelerated area-reaction.

Richet<sup>122</sup> gives a general review of the subject of anaphylaxis and also some very interesting work on anaphylaxis produced by a substance obtained from the *Mytilus edulis*. He found that the blood of a dog sensitized by this substance, when injected into an untreated dog, sensitized the animal two days later to an injection of the extract.

He thinks that anaphylaxis is due to the presence of a toxicogenic substance, non-toxic of itself, but producing a poison by reaction with the second injection of the extract. In support of this view, he states that a mixture of the serum of a sensitized dog and of the extract *in vitro* is more toxic than the extract alone.

Richet<sup>120</sup> reports further experiments on the production of anaphylaxis with an extract prepared from a mussel. (*Mytilus edulis*.)

The experiments were made on dogs, especial study being made of the production of vomiting in the anaphylactic animal.



Vaughan and Wheeler<sup>152</sup> summarize their work to date on the poisonous and non-poisonous portions obtained by splitting proteins. They believe the poisonous group to be an essential constituent of all the protein molecules. It is the chemical nucleus and is regarded as a protein body the chemical structure of which remains unknown. It owes its poisonous action to the avidity with which it combines with certain groups in the molecules that constitute the cells of the respiratory center. The protein molecules of bacteria may thus be broken up, sensitizing the body. The poisonous group, when set free, induces the symptoms of disease and death. Protein susceptibility and immunity are different manifestations of one and the same process; both depend on the development in the animal body of a specific proteolytic ferment. They believe the non-poisonous portion of split proteins to be the immunizing or sensitizing haptophore. The sensitization results in the development of a specific proteolytic ferment. These reactions are specific. The development of a specific zymogen results from an alteration in the atomic arrangement within the protein molecules. Vaughan and Wheeler give a complete bibliography of the work of Vaughan and his pupils on this subject.

Currie<sup>39</sup> studied the effect of repeated injections of horse serum in persons admitted for treatment in the Glasgow Fever and Smallpox Hospital at Belvidere. He concludes that it is apparent from the facts detailed by him that repeated injections of horse serum induce symptoms of supersensitization in man, but it is also apparent that the same facts lend no countenance to the suggestion that the death of persons suffering from diphtheria is to be apprehended as the result of repeated injections of antidiphtheria serum.

Goodall<sup>64</sup> gives observations on ninety patients who had received two injections of horse serum; of these, 43.4 per cent. gave either an immediate or accelerated reaction.

Nicolle<sup>100</sup> found that guinea-pigs were not susceptible to the necrotic action induced by repeated injections of horse serum, as is the case in rabbits. He also found that daily injections or "spaced" injections, after the method of Arthus, did not induce a high degree of hypersensibility in guinea-pigs.

Bienenfeld<sup>25</sup> has studied the leucocytes in the serum disease, and comes to the conclusion that the injection of large quantities of serum has a twofold effect on the number of leucocytes. Immediately following there is a leucopenia, and following this a leucocytosis. The bibliography contains fifty-two references to the literature on this phase of the subject alone.

Friedemann and Isaacs<sup>55</sup> report experiments on the metabolism of proteins introduced into the organism, through channels other than the gastrointestinal tract. The relation to immunity and hypersusceptibility is discussed. Experiments on dogs and goats on nitrogen elimination, after the injection of homologous and heterologous serums, are considered. It is shown that dogs given intravenous injections of 40, 80, or 200 c.c. of egg-white soon die with characteristic symptoms including great muscular weakness and paralysis of respiration.

Heilner<sup>74</sup> considers the effect of large amounts of foreign blood serums introduced into the body by the mouth or subcutaneously. He concludes that the introduction of such foreign serums, and also perhaps other proteins, into the circulation calls forth a certain effort which ordinarily is not present and, further, reports the fact that rabbits are able to withstand, without apparent harm, a single injection of very great quantities of foreign serums—as much as one-eighth of the body weight.

While studying the subject of anaphylaxis in Rio de Janeiro, Vasconcellos<sup>149</sup> found that the guinea-pigs used in Rio, when given a sensitizing dose and, after the usual time, given a second injection, did not show any grave symptoms. He tested the Rio guinea-pigs with the Rio serum as well as with the serum from the Pasteur Institute at Paris, and from *Merck's* and obtained similar results in each case.

In order to see whether this failure of the Rio guinea-pigs to show the reaction of hypersensibility was due to the race of the guinea-pigs, he obtained guinea-pigs from Argentina and found them very susceptible.

He considers that the race of the guinea-pigs plays a considerable rôle in the reaction to a second injection of horse serum.

Weil-Halle and Lemaire<sup>175</sup> prepared an antiserum by injecting horse serum into rabbits and bled the animals when the horse serum as such has disappeared from the blood. Untreated guinea-pigs and rabbits were injected with varying amounts of this antiserum, under the skin of one thigh, and at the same time, with varying amounts of horse serum, under the skin of the opposite thigh. They found that varying with the proportion of the two serums injected, anaphylactic symptoms were produced, either local or general. When local symptoms were produced, they were always at the site of the injection of the antiserum. They believed that the intensity of the reaction seemed to depend on the relation between the quantities of the two serums;

when the quantities approach unity the lesions are more local; when they are wide apart, the general symptoms are more common.

Remlinger,<sup>114</sup> having found in previous experiments that he was unable to produce anaphylaxis in dogs, rabbits and guinea-pigs by the use of rabic virus and sheep serum, endeavored to determine whether this was peculiar to those substances, and if the same results would be obtained with antidiphtheria and antitetanus serums. With these serums, by repeated injections, he obtained no reaction in dogs. In rabbits and guinea-pigs, he obtained the local reactions and only exceptionally the general reactions.

When guinea-pigs and rabbits were given an injection of a mixture of serum and toxin and later injected with normal horse serum, some of the guinea-pigs showed symptoms.

Kinyoun<sup>70a</sup> found that guinea-pigs sensitive to horse serum did not react if they were injected with the blood of a horse which had received several injections of human blood; but that the serum of a horse which had been rendered hemolytic for human red cells, was more toxic than normal serum.

He states that the toxic action is modified by the amount of the sensitizing dose so that the susceptibility is decreased as the amount of serum given at the first injection is increased until one-tenth of the body weight is reached, when they do not respond at all.

He also found that guinea-pigs which had been sensitized with serum did not react to milk.

1908.

Lewis<sup>88</sup> considers that the incubation period of the hypersensitive reaction is not sharply limited, but that there is a progressive increase in sensitiveness from the sixth day, possibly before that, extending over a period of several weeks.

He confirmed our results as to the transmission of the hypersensitive reaction from mother to young, but found that all of the young of sensitive mothers were not equally sensitive. He considered that the anaphylactic state depended on the development of a special antibody during the incubation period, which may be transferred passively to an untreated animal. There is also in the serum of hypersensitive guinea-pigs an uneliminated horse serum element or "rest" which is distinct from the antibody. This antibody may be entirely neutralized by the gradual introduction in twenty-four hours of increasing doses of serum.

Lewis,<sup>89</sup> in his second paper, reports studies chiefly on the hypersusceptibility of young guinea-pigs, born of treated mothers. He found

that when the defibrinated blood of such young guinea-pigs was injected into untreated guinea-pigs, they were rendered hypersensitive to an injection of serum within a few hours, but if the injection of horse serum was delayed until after the incubation period, they failed to react. He discusses in some detail the mechanism of anaphylaxis, holding to the view that the sensitizing injection results in the formation of an antibody.

He also reports some work with a serum which had caused severe symptoms in a man about thirty minutes after injection. He did not find this serum materially different in toxicity from the various normal serums when tested on sensitive guinea-pigs.

By purifying horse serum with ether and then precipitating with ammonium sulphate, Gay and Southard<sup>57</sup> found that, after several precipitations, the last fraction was as highly toxic as horse serum, but distinctly less sensitizing than either whole horse serum or the first fraction. The first fraction, obtained by one-third saturation with ammonium sulphate (euglobulins), is as highly sensitizing as whole horse serum; it is analogous to anaphylactin and apparently a purely sensitizing substance without admixture of the toxic elements of horse serum. This euglobulin is absolutely non-toxic for sensitive animals. Repeated large doses not only cause no refractory phase but shorten the period of incubation. It sensitizes normal animals in a few days (four or five).

Gay and Southard<sup>58</sup> state that increased susceptibility in sensitized animals is due to the continued presence in the circulation of an unneutralized element of horse serum (anaphylactin), which acts as an irritant or stimulant to the body cells and in some way causes them to assimilate over-rapidly certain other elements of horse serum. They believe that anaphylactin is not an antibody to horse serum, but some retained substance. They also express the belief that the intoxication of animals by horse serum is not due to a toxic substance formed of antibodies plus antigen and that moreover the reaction of intoxication takes place, not in the circulation of the animal, but in the prepared cell.

Gay and Southard<sup>59</sup> emphasize the point that a sensitive animal intoxicated with a large dose of serum and recovering passes thereby into a refractory state (antianaphylaxis), and by the same mechanism again becomes sensitive to the toxic effects of horse serum.

Gay and Southard<sup>61</sup> state that animals sensitized with either egg-white or milk will react more or less characteristically to horse serum. After sensitization with egg-white guinea-pigs will react faintly to

milk; after sensitization to milk they will react slightly to egg-white. They conclude from this that anaphylaxis is only relatively specific.

Gay and Southard<sup>62</sup> found macroscopic hemorrhages in one or more organs in 85 per cent. of the guinea-pigs which either died of a second dose of horse serum or were killed within twenty-four hours after the second injection. The cause of death, when it occurs, is respiratory. Respiration ceases in the inspiratory phase and shows itself anatomically and histologically as emphysema. The most striking functional feature is severe diaphragmatic spasm. The application of horse serum to the exposed vagus of a sensitive guinea-pig produces severe respiratory symptoms. Gay and Southard regard the changes in the respiratory centers as a physical rather than as a chemical nature. They state that neither hemorrhage nor respiratory death is an indispensable feature of this disease. All guinea-pigs so far examined show fatty changes in many regions involving single muscle fibers or other cells.

Rosenau and Anderson<sup>6, 136</sup> report the results of further studies on anaphylaxis. It is shown that the period of incubation is about seven days in guinea-pigs sensitized in the brain and about nine days in guinea-pigs sensitized subcutaneously. It also appears that the sensitization comes on somewhat gradually. The period of incubation is quite constant and is not appreciably prolonged by a large sensitizing dose. Sensitized guinea-pigs probably remain sensitive throughout the rest of their lives, at least 732 days.

The effect of heat and chemical substances is again studied in relation to the sensitizing and toxic principles in horse serum. The specific nature of anaphylaxis is further shown by various experiments. Three separate anaphylactins have been demonstrated in the blood of a guinea-pig. It is shown that the substance known as anaphylactin is not present during the period of incubation; and may be demonstrated in the blood serum of immune guinea-pigs. Congestion and hemorrhages are sometimes found in guinea-pigs dead of anaphylaxis. Fatty lesions were not discovered. These morphologic alterations, it is believed, do not explain the mechanism of anaphylaxis.

It is shown that horse serum used in cases followed by sudden death in man is no more toxic for guinea-pigs than antitoxic horse serum used extensively in human therapy without untoward symptoms. The belief is expressed that it is not the special toxicity of the horse serum, but the sensitization of the patient, which accounts for the collapse or sudden death sometimes following the injection of horse serum. The essential lesion in serum anaphylaxis is probably localized in

the respiratory center, and the association of asthma with hypersusceptibility to horse serum must be considered in the use of antitoxin. A relation between the toxemias of pregnancy and anaphylaxis is suggested.

It is shown by Rosenau and Anderson<sup>135</sup> that guinea-pigs can not be sensitized with guinea-pig fetal blood. Female guinea-pigs, however, may be sensitized with placental extract. After an interval of twenty-two days or longer they show symptoms of protein anaphylaxis when given a second injection of guinea-pig placental extract. It therefore seems that the mother guinea-pig may be sensitized with the autolytic products of her own placenta. These experiments suggest that there may be a certain relation between some cases of puerperal eclampsia and the phenomenon in the guinea-pig.

Besredka<sup>20</sup> confirmed the results reported by Rosenau and Anderson, that guinea-pigs are easily sensitized to a second injection of milk. He found that they responded markedly to a second injection when given into the brain, and that guinea-pigs which had been injected with other substances than milk at the first injection, supported without ill effects an intracerebral injection of 0.25 c.c. of milk, thus showing the specificity of the reaction.

He found that when milk had undergone the lactic acid fermentation, the curd contained the sensitizing, as well as the toxic properties of the milk, while the whey (*petit lait*), even when given into the brain, failed to cause symptoms in a sensitive guinea-pig.

Besredka<sup>21</sup> refers to his preliminary note on the same subject in which he brings forth his ideas as to the presence in normal serum of the two substances, *sensibilisinogène* and *antisensibilisine* and the properties and action of the two.

In his later article, he gives the details of his experiments on which he bases his conclusions. He believes, as stated in his first paper on the same subject, that it is the combination of the *sensibilisine* and the *antisensibilisine* in the nucleus of the nerve cells that produce the anaphylactic shock. This shock may be lessened either by large doses given during the period of incubation, or by small repeated doses after the period of incubation, so that this union of the *sensibilisine* and *antisensibilisine* takes place more slowly.

The shock may also be lessened by rendering the nerve cells indifferent to this brusque union, as by ether narcosis. Antianaphylaxis is due to a desensitization, followed by a return of the guinea-pig to a normal state. If the antianaphylaxis is not definite, following a large injection of the serum, it is because the surplus of *sensibilisino-*

*gène*, which remains after the elimination of the *antisensibilisine*, is capable of resensitizing the animal.

Wells<sup>177</sup> suggests that the toxic effect of a second dose of protein injected into an animal that has been sensitized by an injection of the same protein two weeks or more previously, may be dependent on the aromatic radicals of the protein.

Wells<sup>178</sup> in a most interesting article takes up a study of the chemistry of the substances involved in anaphylaxis and the chemistry of the reaction itself. The major portion of his work was with pure egg-albumin, purified by repeated crystallization. He found that this pure egg-albumin would sensitize guinea-pigs in doses of one-twenty-millionth of a gram; fatally, in doses of one-millionth of a gram. The minimum fatal dose for sensitized guinea-pigs, given intraperitoneally, was about 0.5 milligram, and about 0.1 to 0.05 milligram when injected into the circulation. As so small a quantity, 0.1 milligram, of pure egg-albumin is fatal for sensitized guinea-pigs, he thought it improbable that the injected protein itself could cause death by splitting up and liberating poisonous substance in the space of time in which the reaction occurs. He thought that the minuteness of the minimum sensitizing and intoxicating doses of pure egg-albumin seemed to indicate conclusively that, at least with this protein, both the sensitizing and intoxicating agents were one and the same kind of protein molecule, or else two different proteins of the same molecule.

He found that milk did not lose its sensitizing and intoxicating power when heated to 100 degrees for thirty minutes, and inclined to the belief that this might be due to the fact that the caseinogen of milk is not coagulated by boiling.

Iodization of serum and pure egg-albumin did not alter the specificity of the reaction when these substances were used on guinea-pigs.

Nicolle, Nicolle and Pozerski and Nicolle and Abt published three articles early in 1908 which may be reviewed together.<sup>102</sup> We can not here follow these authors fully in detail and must satisfy ourselves with citing the principal points. The facts of protein hypersusceptibility are explained as follows:

The substance injected contains a toxic element which is set free by specific antibodies in the hypersusceptible animal. Hypersusceptibility may be produced by developing this antibody, to which the authors give the general name of lysin; thus, toxolysin, albuminolysin and cytolyisin. They assume that a coagulation caused by another antibody is necessary. This antibody is called the coagulin; thus, toxocoagulin, albuminocoagulin, cytoagulin. All the antigens produce antibodies

at the same time. Depending on their respective quantities, there is either hypersusceptibility or immunity. The order of events following a reaction would be: First, the fixation of the antibody by the antigen, then the coagulation of the antigen, then the slow and silent destruction by the lysin.

These antibodies have not yet been demonstrated *in vivo* or *in vitro*; but the authors state that there is no reason why they may not exist as precipitins, acting only *in vitro*.

Hypersusceptibility occurs when there is a rapid lysis of a sufficient quantity of antigen. On the other hand, immunity manifests itself when there is first coagulation of the antigen. The lysis then follows slowly, liberating a little of the poison at a time. The two phenomena may coexist.

Otto<sup>106</sup> gives a comprehensive review of the work on anaphylaxis and the serum disease to date. He discusses the historical development of the subject,—the serum disease in man, experimental anaphylaxis especially in guinea-pigs, and concludes with an admirable review of the theories which have thus far been brought forward to explain hypersusceptibility. The bibliography contains seventy references to the literature on the subject.

Richet<sup>124</sup> in studying the anaphylactic properties of actino-congestine, suggests as a rational theory that the injection of the actino-congestine causes at the end of about two weeks (period of incubation) the formation of a new substance, which he calls *toxogénine*, which alone is harmless, but in the presence of the original poison becomes hypertoxic.

In this article he gives some interesting details of experiments on dogs, in which, by injecting untreated dogs with the serum of treated dogs, he was able to render the untreated animals very susceptible to a first injection of actino-congestine.

Hamman<sup>72</sup> states that the views of Wolff-Eisner seem to fit best into what we at present know of the tuberculin reaction and, shorn of their technicality, are briefly this: Tuberculin, which really consists of ultramicroscopic portions of the tubercle bacillus, produces the same effects in the animal body as the tubercle bacilli, except that the latter are capable of multiplication. The local tuberculin reaction is caused by an accumulation of lymphoid cells, and true giant cells are formed. The injection of living tubercle bacilli is followed by the development of hypersensitiveness the same as that which follows tuberculin injections. As in typhoid and cholera, the immunity reaction in tuberculosis depends on the presence of lysins. The tuberculin



reaction is not due to the tuberculin itself nor to the disintegration at the site of disease, but to a new toxic substance formed by the action of the lysins on the albuminous portion of the bacillary body. For this toxic substance to become active the organism must be in a condition of hypersensitiveness. There are, then, two factors to be considered; the presence of lysins and the condition of hypersusceptibility. The lysins may be artificially increased and are the bodies which deviate complement in Wassermann's experiment. The hypersensitiveness varies under conditions of which we are still ignorant, but it, too, may to some extent be stimulated or blunted. Normally there is no lysin present, or so small an amount that when tuberculin is injected the transformation goes on so slowly that the newly formed toxin causes no appreciable effect. Under continuous minimal stimulation the quantity of lysin increases, and the transformation then occurs so rapidly that after injection intense toxic symptoms occur. The toxin causes a local reaction at the site of injection, constitutional symptoms and an inflammatory reaction at the site of the tuberculous lesion. During the inoculation of small doses of tuberculin hypersensitiveness is developed. Variation in susceptibility to tuberculin in tuberculous subjects depends essentially on variation in hypersensitiveness, lysins probably being present in all.

Weil-Halle and Lemaire<sup>170</sup> found that if untreated guinea-pigs were injected at the same time with 0.01 c.c. of horse serum and 4 c.c. of the serum of a rabbit, which had previously been given horse serum, many of the guinea-pigs died in from eight to fifteen days. If the rabbit was bled in less than ten days or after sixty days, no ill effect was caused by the injections.

Remlinger<sup>115</sup> having noticed that the injection of one large dose or several repeated small doses of the nervous tissue of the brain of different species produced in certain animals emaciation, cachexia and even death, endeavored to determine if this was due to an anaphylactic action of the nerve substance.

He injected dogs at intervals of ten to fifteen days subcutaneously with nerve tissue from the rabbit; guinea-pigs, with rabbit nerve tissue, and rabbits, with either rabbit, guinea-pig or dog nerve substance. After a variable number of injections, they were all tested by the intracerebral injections of the nerve substance of the same species used in the preliminary treatment. He never noticed the least morbid phenomenon.

These results are open to the criticism that the use of several injections, especially in the guinea-pig, may have immunized the animals to the test injection.

Grunbaum<sup>65</sup> reports some observations in eleven cases in which antituberculosis serum had been administered. In no case did the second injection cause any uncomfortable effect: the fourth injection, in one case, was followed by an urticarial eruption; in another case, edema of the tongue and larynx followed two successive injections, and in a man thirty-one years of age, the twentieth injection was followed almost at once by cyanosis, vomiting, collapse and death in five minutes.

Grunbaum attributes these accidents to an individual susceptibility.

Banzhaf and Famulener<sup>12</sup> found that anaphylactic symptoms could not be prevented by ether narcosis, morphin sulphate or calcium chlorid. They found that if chloral hydrate was used to produce hypnosis in sensitive guinea-pigs, about 75 per cent. were completely protected against the injection intraperitoneally of 5 c.c. of serum, while 90 per cent. of the controls died.

Pozerski<sup>110</sup> found that repeated injection of papain into guinea-pigs, very much less than the minimum lethal dose, at intervals of four or five days, produced after the third, fourth or fifth injection an undoubted state of anaphylaxis with death, accompanied by the same postmortem appearances as found in death from a single large dose.

Moro<sup>96</sup> assumes that the percutaneous reaction is a late reflex; that is, an angioneurotic inflammation. This view is confirmed by the fact that the reaction occurs at other points of the body than where the tuberculin lanolin is applied. The cutaneous reaction is often symmetric and suggests, according to Moro, hypersusceptibility of the sympathetic nervous system.

Gillette<sup>93</sup> reports sudden death in an asthmatic following the injection, five minutes previously, of 2,000 units of diphtheria antitoxin. The postmortem failed to shed any light on the case.

#### SYMPTOMS CAUSED BY THE INJECTION OF HORSE SERUM INTO A SENSITIZED GUINEA-PIG

Very characteristic symptoms are produced by horse serum, either normal or antitoxic, when injected into a susceptible guinea-pig. The symptoms are apparently the same whether the injection is made subcutaneously or into the peritoneum, or whether normal or antitoxic serum is used. In five or ten minutes after injection the pig becomes restless and agitated; then manifests indications of peripheral irritation or respiratory embarrassment by scratching at the mouth, coughing, and sometimes by spasmodic, rapid or irregular breathing. This

stage of exhilaration is soon followed by one of paresis or complete paralysis. The pig is unable to stand, or, if it attempts to move, falls on its side; when taken up it is limp. Spasmodic, jerky, and convulsive movements now supervene.

Pigs in this state with complete paralysis may fully recover; but usually convulsions appear, and are almost invariably forerunners of death. Symptoms appear in about ten minutes after the injection has been given; occasionally in pigs not very susceptible they are delayed thirty to forty-five minutes. Only in one or two instances of the many hundred pigs which we have observed have the symptoms developed after one hour. Pigs developing symptoms as late as this are not very susceptible and do not die. The chain of symptoms is exceedingly characteristic. The symptoms do not always follow in the order given. Death usually occurs within an hour and frequently in less than thirty minutes.

If the second injection be made directly into the brain the symptoms are manifested with explosive violence, the animal frequently dying within two or three minutes. The same is also true if the second injection be made directly into the circulation.

We took the temperature of a number of guinea-pigs twice daily for eighteen days following the injection of large quantities of horse serum subcutaneously, in order to determine whether a febrile reaction followed. No marked deviation from the normal temperature was noted.

Normal horse serum, when injected into normal guinea-pigs, causes no symptoms. Large amounts, such as 6 or 10 c.c., may be injected into the peritoneal cavity of a guinea-pig without any apparent inconvenience to the animal. When normal horse serum is injected subcutaneously into the guinea-pig it is sometimes either absorbed very slowly or there is a slight local reaction, as indicated by edema and induration of the subcutaneous tissue at the site of inoculation.

#### THE POISON ACTS ON THE RESPIRATORY CENTER

Judging from the symptoms produced by the injection of horse serum into a susceptible guinea-pig we assumed that the poison acted on the central nervous system. Autopsies done immediately after the death of the guinea-pigs showed invariably that the heart continued to beat after respiration had ceased. In some instances the heart would continue to beat a full hour when exposed. This would seem to indicate that we were dealing with a poison which caused death through the nervous control of the respiration, and experiments show that this effect is certainly not local.

## PERIOD OF INCUBATION

A certain time must elapse between the first and the second injection of the foreign protein before the toxic action is manifest. This period of incubation is from seven to twelve days and corresponds suggestively with the period of incubation of the serum disease, which von Pirquet and Schick place at eight to thirteen days, and with the period of incubation of some of the infectious diseases.

If a guinea-pig be given an injection of serum and then be injected again any time during the period of incubation no ill results follow. In other words, the animal has not had time to enter a state of anaphylaxis to the foreign protein. If, however, the injection be given after the seventh to the twelfth day the animal is then in a state of anaphylaxis or hypersusceptibility to the foreign protein. The animal remains susceptible a very long time. The longest period which we have observed is 732 days between the first and the second injection. There is no reason to doubt that guinea-pigs remain susceptible during their entire lives.

We found that the period of incubation appeared about the seventh day in guinea-pigs sensitized in the brain and about the ninth day in guinea-pigs sensitized subcutaneously. So far as may be judged, it therefore appears that the period of incubation is somewhat shorter in guinea-pigs sensitized in the brain than in those sensitized subcutaneously. It also seems quite evident that the sensitization comes on somewhat gradually. Judged by our results and the work of others the period of incubation is quite constant.

Lewis states that the period of incubation is not to be considered as abruptly terminating at a given day. He says that he has made an animal quite sick by the intracardial injection of 2 c.c. of serum on the sixth day after the toxin-antitoxin mixture. We have obtained suggestive symptoms on the fourth and the fifth day.

So far as may be judged from our work, the period of incubation is not appreciably prolonged by a large sensitizing dose.

## THE SENSITIZING SUBSTANCE

We have suggested that the protein which sensitizes the guinea-pig is the same as that which later poisons it; profound changes are produced by the first injection. These changes localize themselves in the central nerve cells at the second injection. Our subsequent work has evolved nothing to alter this working hypothesis.

Guinea-pigs may be sensitized by administering the foreign protein subcutaneously, intraperitoneally, intracerebrally, directly into the circulation, or by feeding.

We have shown that the filtrate from horse serum, after precipitation with ammonium sulphate, still possesses sensitizing powers in spite of the fact that this filtrate contains but little of the serum globulin and is very weak in antitoxic value.

Formaldehyd does not appear to modify the sensitizing property in horse serum, though it is capable of destroying the toxic properties of tetanus<sup>5</sup> and diphtheria toxins.

From a limited number of experiments it seems that the sensitizing principle is not dialyzable through a collodion sac when placed in the peritoneal cavity of a guinea-pig.

The sensitizing principle is not affected by the various preservatives used for the preservation of antitoxic serum, by drying, by precipitation with ammonium or magnesium sulphate, or by admixture with diphtheria or tetanus toxins.

The removal of the spleen or the thyroid from the animal before or after receiving the sensitizing dose apparently has no effect on the development of anaphylaxis.

We have found that the sensitizing principle of horse serum is gradually influenced by heat and almost entirely disappears when the liquid serum is heated to 100° C. for one hour. Pigs sensitized with small quantities of horse serum heated to 100° C. for one hour, when subsequently tested, develop very slight symptoms.

Guinea-pigs may readily be sensitized by intracerebral injections, provided quantities of 0.0001 c.c. or more are used. We obtained negative results with sensitizing doses of 0.00001 c.c.

The blood serum or an emulsion of the brain substance of a sensitized guinea-pig, when mixed with horse serum, does not modify the sensitizing power of the horse serum.

Some breeds of guinea-pigs appear to be more susceptible than others. The American guinea-pigs seem to be most susceptible, the German breeds not quite so much, and the French somewhat less, while the guinea-pigs tested by Vasconcellos in Rio de Janeiro scarcely respond at all.

#### THE TOXIC PRINCIPLE

At one time we made efforts to isolate the active principle in horse serum which causes the symptoms, but as soon as we realized that the toxic principle present in horse serum exerted its action in quantities so minute as to place it almost in the category with the ferments, we realized how difficult it would be, with the present technic, to isolate this substance. Nevertheless, we devoted much time and study to the relation of this toxic principle to various chemical, physical, and elec-

trical influences. The practical importance of eliminating this toxic principle from horse serum, or of neutralizing it, is at once evident.

The toxic principle is not affected by various chemicals, such as calcium chlorid, sodium nitrate, magnesium sulphate, ammonium sulphate and formaldehyd.<sup>5</sup> It is not affected by various ferments, alkaloids and similar substances, such as *takadiastase*, pancreatin, rennin, myrosin, invertin, emulsin, pepsin in acid solution and in alkaline solution, *inglurin*, malt, atropin, strychnin, morphin and caffenin.

It is not affected by freezing at 15 degrees F., or by filtration through porcelain, drying, precipitation and dialysis, or exposure to the x-rays.

We found it interesting to compare the toxic effects on sensitive animals of untreated antitoxic serum, and the precipitated refined antitoxin; bulk for bulk we found them equally toxic. But as the same number of units can be given in half the bulk there is a manifest advantage in using the precipitated serum, as the rashes and other untoward effects of serum depend to some extent on the volume of serum administered.

The smallest amount of serum given intraperitoneally that we have found to cause the death of a guinea-pig is 0.1 c.c. One hundredth of a cubic centimeter, when given directly into the heart, is sufficient to cause the death of the animal, while 0.25 c.c. given into the brain is almost invariably fatal. In most of our work, however, we have used 5 or 6 c.c. of serum intraperitoneally, and this seems to be the favorite dose of other workers. Certain symptoms in guinea-pigs caused by a second injection of the serum suggested to us that the action might be due to hemolysis or the formation of precipitins. By a large number of experiments, however, we were able to exclude both hemolysis and the formation of precipitins as factors.

Sensitized animals were given various chemicals the day before the second injection of serum. No influence on the anaphylactic state was obtained by these substances. The following were used: pancreatin, potassium oxalate, sodium sulphate, magnesium sulphate, peptone, calcium chlorid and calcium acetate.

Obermayer and Pick find that when the aromatic radicals of a protein are combined with various substances the protein loses the power to produce precipitins of closely allied specificity for the original species. Their results suggest that the aromatic groups of the molecule are closely related to the species specificity. This indicates that the striking specificity of proteins of different species depends on the

aromatic groups of the protein molecule and Vaughan has found evidence that the toxicity of the proteins depends on these same groups.

Fleischmann also finds that tryptic digestion destroys this characteristic species specificity.

We tested a large number of guinea-pigs to determine this point but found that, so far as the toxicity of horse serum is concerned at the second injection, it was not appreciably modified by iodine.

A few experiments were made to determine the relation of meta-hemoglobin-producing substances, such as nitrates, on the symptoms. Sensitive guinea-pigs were given subcutaneously an injection of sodium nitrite. In thirty minutes the exposed mucous membranes appeared distinctly blue; they were then tested for their susceptibility to horse serum and found to react in the usual way. Controls showed that the quantity of nitrite used was not sufficient in itself to kill the guinea-pigs.

Besredka reported some interesting observations concerning the prevention of anaphylaxis by ether narcosis. He stated that if sensitive guinea-pigs were etherized to the stage of complete relaxation and while in this state injected intracerebrally with normal horse serum, and the administration of ether continued a short time, the animal continued to sleep after the injection and at the end of about a half an hour awoke without presenting the least symptoms of anaphylaxis. If the guinea-pig were tested on the following day it would be found to be immune.

Of eight guinea-pigs on which we tried this experiment with ether, seven died from the effects of the second injection of horse serum. It is our belief that the guinea-pig which recovered had masked symptoms while under the influence of the ether and probably would not have died in any case, for we have a certain number of recoveries from the intracerebral injections of 0.2 c.c. of horse serum. It is true, however, that the narcosis masks the symptoms. The difference in our results may be accounted for either by the difference in toxicity of the French and the American serums, or, more likely, by the difference in susceptibility of the animals used.

Normal horse serum may be heated to 90 degrees C. for one hour and still remain slightly toxic when injected into a sensitized guinea-pig. Its toxicity, however, is evidently markedly affected. Heating to 70 degrees C. for one hour does not seem to diminish appreciably its poisonous properties, but it appears to be affected at 80 degrees C. for one hour. At 100 degrees C. for one hour the toxicity apparently disappears.

It appears that there is a slight difference between the sensitizing and toxic principles in horse serum so far as the resistance to heat is concerned. Serum heated to 100 degrees C. for one hour retains some power of sensitization, but seems to lose its toxicity when given at the second injection. This difference may be more apparent than real, for exceedingly minute amounts are sufficient to sensitize guinea-pigs, while a very large quantity of weakened serum would be necessary to produce symptoms. It must be remembered that in our experiments 20 c.c. of the dilution represents but 5 c.c. of serum.

These facts must be kept in mind when drawing conclusions from work on split proteins, fractional precipitation, or other methods to isolate the sensitizing substance in pure form. A very minute amount of the original protein substance in horse serum clinging to the globulin, or other substances modified by chemical methods, might be sufficient to sensitize guinea-pigs, whereas it would require very large amounts of such a modified protein to poison a sensitive animal.

#### THE SPECIFIC NATURE OF ANAPHYLAXIS

From our first studies upon hypersusceptibility we were interested in the question whether this reaction was specific.

In our first work on this subject we showed that this reaction was quantitatively specific for serums. That is, guinea-pigs sensitized with horse serum are subsequently very susceptible to a second injection of horse serum, but only slightly if at all susceptible to a second injection of the serum of other animals, such as rabbit, cat, dog, hog, sheep, chicken, or man. Conversely, guinea-pigs sensitized with the serum of these other animals are not very sensitive to a second injection of horse serum, whereas they respond actively to a subsequent injection of the same kind of serum as that used for the first injection.

We have further shown that the specific nature of this phenomenon is more marked when protein substances of widely different nature are used at the first and second injections. Thus, a guinea-pig sensitized with horse serum does not react at all to a subsequent injection of egg-white, vegetable protein, or milk. A guinea-pig sensitized with milk does not react to the other protein substances mentioned, etc.

We have succeeded in demonstrating more clearly the specific character of the phenomenon we are studying by proving that guinea-pigs may be in a condition of anaphylaxis to three protein substances at the same time. For instance, a guinea-pig may be sensitized with egg-white, milk, and horse serum, and may subsequently react to a second injection of each of these substances within a brief period of time. The



guinea-pig may be sensitized by injecting these strange proteins either at the same time or at different times, in the same place or in different places, or by injecting them separately or mixed. The guinea-pig differentiates each anaphylactic-producing protein in a perfectly distinct and separate manner. The animal is susceptible to the second injection of each one of the three substances in the same sense that it is susceptible to three separate diseases. These distinct reactions, in so brief a time, seem to accentuate the specific nature of the phenomenon we are studying. It also adds weight to our belief that profound chemical changes, probably in the central nervous system, rather than morphologic alterations explain the essential features of the reaction.

Further evidence on the specific nature of the phenomenon will be found in the discussion of anaphylactin.

#### ANAPHYLACTIN

Gay and Southard first discovered the interesting fact that if the blood of a guinea-pig which has received a small sensitizing dose of normal horse serum be drawn, the serum collected, and 1.5 c.c. of this be given to a normal guinea-pig, the animal is rendered susceptible to a subsequent injection of horse serum fifteen days later.

Otto then showed that the animals react if tested within twenty-four hours.

Gay and Southard applied the name "anaphylactin" to this substance in the blood of sensitized guinea-pigs. They considered this substance a portion or "rest" of horse serum.

The sensitizing substance or anaphylactin (called *sensibilisinogène* by Besredka) is present in the blood serum of a sensitive animal. We have limited the word anaphylactin to indicate that substance in the blood serum of a sensitive animal which, when transferred into a normal animal, is capable of sensitizing it within forty-eight hours. It must be present in an exceedingly minute amount, for we have shown that the blood of guinea-pigs receiving only 0.002 c.c. of serum contains this substance several months later, and 1.5 of the serum of such animal, when injected into a normal animal, renders it sensitive to a subsequent injection of horse serum twenty-four hours later.

It is of some interest to determine just when anaphylactin appears in the blood of a sensitized guinea-pig, particularly whether its presence may be demonstrated during the period of incubation. We found no indication of this substance in the blood of sensitized guinea-pigs until the ninth or tenth day, i. e., just about the time necessary to render guinea-pigs sensitive.

We have found that anaphylactin is present in the blood serum of immune guinea-pigs. This fact is of importance in the consideration of the mechanism of anaphylaxis. From this we may argue that a true condition of immunity exists, for the sensitizing substance is certainly present in the flowing blood, but the organism as a whole or its susceptible cells are protected by a neutralizing antibody.

We have referred above to the fact that guinea-pigs may be in a condition of anaphylaxis to three protein substances at the same time. We later found that the substance in the blood serum of sensitized guinea-pigs known as anaphylactin is also specific in the same sense. By transfusing the blood serum of guinea-pigs sensitized to horse serum, egg-white, and milk, three separate and distinct reactions were obtained in the guinea-pig into which this serum was transferred.

#### LESIONS

Gay and Southard, 1907, found lesions in guinea-pigs dying from a second injection of serum, and in those which had severe symptoms and were later chloroformed, which they interpreted as explaining the mechanism of anaphylaxis. They state that, "the study of the histopathology of this serum disease shows us that we have to deal with an intimate cell reaction, demonstrable by definite cell lesions." These investigators state that considerable hemorrhages, rather definitely localized, are the characteristic gross lesions. The hemorrhages may be in one or several organs, gastric hemorrhages being especially frequent. Microscopically, there are, in addition to the naked-eye hemorrhages, minute interstitial and oozing hemorrhages. They also found fatty changes in voluntary muscle fiber, heart muscle fiber, and in nerve fiber.

That the congestion and dilatation of the blood vessels found in the abdominal cavity and the hemorrhages on the mucosa of the stomach are not characteristic of death due to anaphylaxis is evident from the fact that we have found that in violent death produced by large subcutaneous injections of chloral cyanhydrin or hydrocyanic acid there are somewhat similar congestions and hemorrhages. Further, we have lately had the opportunity to examine a guinea-pig whose death was caused by suffocation in an atmosphere of carbon dioxide. In the stomach and lungs of this guinea-pig lesions were found that, so far as the congestion and hemorrhages are concerned, were similar to those described in guinea-pigs dying from a second injection of horse serum.

We were especially struck by the fact that macroscopic congestions and hemorrhages were frequently absent in guinea-pigs poisoned by a second injection of horse serum given into the brain.

Finally, this congestion and dilatation of the vessels of the abdominal cavity is well known to occur in shock and other states.

We were unable to confirm Gay and Southard's findings in regard to the fatty changes.

It is noticeable that one of the conspicuous lesions of the serum disease and other reactions to foreign proteins consists of an angioneurotic edema. In serum anaphylaxis as seen in the guinea-pig the irritation of the skin and mucous membranes of the mouth may be of the nature of an angioneurotic edema. One might imagine a localized edema of this character in the ganglia about the respiratory centers to account for the serious symptoms or death.

#### FEEDING EXPERIMENTS

Guinea-pigs may be sensitized by feeding them meat or serum.

We found that guinea-pigs could be sensitized by feeding them for some days on horse meat, or dried horse serum, mixed with their food. We did not use a stomach-tube, as the possibility of making slight wounds in the esophageal or gastric mucosa would vitiate the feeding experiments, as we know from our previous work that very small quantities could readily sensitize the animal to a subsequent injection of serum.

The guinea-pigs that had been fed with horse meat or horse serum, after an interval of at least four days, were injected with horse serum and reacted in a characteristic manner.

We also found that guinea-pigs could be sensitized to cattle serum by feeding them with beef. Cooking the meat entirely destroyed its sensitizing properties.

The fact that guinea-pigs may be rendered susceptible by the feeding of strange protein matter opens an interesting question as to whether sensitive guinea-pigs may also be poisoned by feeding with the same serum given after a proper interval of time. If man can be sensitized in a similar way by the eating of certain protein substances, may not this throw light on those interesting and obscure cases in which the eating of fish, sea food, and other articles of diet habitually cause sudden and sometimes serious symptoms?

#### MATERNAL TRANSMISSION

In the course of our work we had the opportunity to test the susceptibility of the young of susceptible guinea-pigs and we found that hypersusceptibility to the toxic action of horse serum is transmitted from the mother guinea-pig to her young. This function is solely maternal;

the male takes no part whatever in the transmission of these acquired properties. Whether this maternal transmission is hereditary or congenital can not be definitely stated.

We were able to exclude the milk as a factor in transmitting the hypersusceptibility to the toxic action of horse serum by a series of "exchange" experiments. Exchange experiments consist in at once placing guinea-pigs born of a susceptible mother to nurse with an untreated female while, in exchange, the young of the untreated female are placed to nurse with the susceptible female. From these exchange experiments we learn that the hypersusceptibility is not transmitted to the young in the milk.

We also learned from our experiments that hypersusceptibility may be transmitted from mother to young, whether the mother is sensitized before or after conception.

If an anaphylactic tendency be transmitted from mother to young in man it may explain the severe reaction and death that occasionally take place following a first injection of serum.

These results on the hereditary transmission of the susceptibility to the poisonous action of horse serum in guinea-pigs may throw light on the well-known inherited tendency to tuberculosis in children born of a tuberculous parent.

There are certain analogies between the action of tuberculosis and horse serum. Both produce hypersensitiveness and also a certain degree of immunity. Now that we have proved that this hypersensitiveness or anaphylactic action in the case of horse serum may be transmitted hereditarily in guinea-pigs, may it not throw light upon the fact that tuberculosis "runs in families"? While there are several recorded instances demonstrating that immunity to certain infectious diseases may be transmitted from a mother to her young, this is, so far as we know, the first recorded instance in which hypersensitiveness, or a tendency to a disease, has been experimentally shown to be transmitted from a mother to her young.

#### IMMUNITY TO ANAPHYLAXIS

We showed in our first publication on the subject of anaphylaxis that guinea-pigs may be actively immunized against this phenomenon. At the same time we demonstrated that the immunity could not be transferred passively to other animals in the blood or body juices.

Guinea-pigs may be actively immunized in several ways: (1) by repeated injections of serum during the period of incubation, i. e., during the first ten days, before the animal reaches the state of hyper-

susceptibility; (2) animals that recover from a second injection given during the anaphylactic stage are at once immune.

The fact that guinea-pigs can not be immunized passively by the transfer of blood or body juices would make it appear that the "immune body," if such exists against the toxic action of horse serum, is not free in the blood or body juices as is the case in diphtheria. In fact, it has been questioned whether the active immunity which we have described is an instance of true immunity, or a "refractory" condition, or even an actual return to the normal.

Subsequent researches have strengthened our belief that we are dealing with a true condition of immunity and not a prolongation of the period of incubation or a return to the normal. Thus, it has been shown that guinea-pigs in the "refractory" condition still contain anaphylactin in their blood. It is at once evident that they have not returned to their normal condition. Further, we have demonstrated that such "refractory" female guinea-pigs will transmit this anaphylactic substance to their young. Only the sensitizing substance passes into the blood of the fetus, which is therefore in a condition of hypersensibility. The "immunizing substance" or "condition" is not transmitted.

It seems to us that we have here a striking analogy to that phase or kind of immunity which von Pirquet describes as "allergie." In other words, we have an acquired immunity associated with anaphylaxis. In guinea-pigs this immunity may follow one attack of the disease, i. e., the serum reaction. As stated by von Pirquet, "allergie" manifests itself by an immediate reaction and corresponds to the condition of immunity conferred by an attack of smallpox or some of the other acute infectious processes.

In the case of syphilis we have a striking instance in which the virus is not autoinoculable. In the serum reaction in the guinea-pig an analogous train of events occurs, for after the sensitized guinea-pig has responded the reaction renders the organism immune.

#### ACTION OF HORSE SERUM ON MAN AND OTHER ANIMALS

It may be that man can not be sensitized in the same way that, as we have shown, guinea-pigs can. We made no human experiments, but experimental data are recorded by others which have a direct bearing on this question.

Repeated injections of horse serum into man is not an infrequent occurrence. Patients suffering from diphtheria are often given injections of antitoxic serum at short and frequent intervals. It is also

not rare for persons to have several attacks of diphtheria at long intervals and to be treated each time with antidiphtheria serum.

Certain serums, for example the antitubercle serum of Maragliano or the antirheumatic serum of Menzer, are habitually used by injections at intervals of days or weeks.

In all these cases of frequent or repeated injections the amount which has been injected and the interval between the injections must be taken into account in relation to this work. Von Pirquet and Schiek, in their work on *Serumkrankheit*, give eight instances in which children received two injections of horse serum at intervals of sixteen to forty-two days between the first and the second injections. All these eight cases show this in common, that after the first injection of horse serum the symptoms of the serum disease appear after the normal period of incubation, i. e., between the eighth and the thirteenth day. But when the individuals are again injected with horse serum after intervals of sixteen to forty-two days symptoms of the serum disease reappear at once or at least within twenty-four hours.

Von Pirquet and Schiek give a list of 60 children who were injected with antitoxie horse serum at intervals of six days to seven and a half years between the first and the second injections. They found that when the second injection was given from fourteen days to four months after the first injection they obtained, with great regularity, what they termed the "immediate reaction"; but when the interval between the first and second injections is over four months they obtained little or no immediate reaction but what they termed "an accelerated reaction," for the fever, urticaria and other symptoms of the disease appeared on the fifth, sixth, seventh, or eighth day. It will be remembered that the normal period of incubation for the symptoms of the serum disease to appear after the first injection is between the eighth and the thirteenth day. Von Pirquet and Schiek lay special stress on the phenomenon of the "immediate" and the "accelerated" reactions following the second injection.

We might also conclude, despite the suggestion in our work on sensitizing guinea-pigs by feeding them with horse serum or horse meat, that children are not sensitized to the toxie action in horse serum by eating horse meat, from the fact that horse meat is a favorite article of diet in certain European countries, and that there is nothing on record to show that the injection of horse serum in those countries is fraught with more danger than where this practice does not obtain. We must, however, remember that our work has shown that guinea-pigs are sensitized with exceedingly minute quantities of the strange

protein, and that repeated injections cause an immunity; and it is possible that the same may be true of feeding. Further, we have shown that cooking destroys the sensitizing property of meat.

Man reacts to the first injection of horse serum after a period of incubation of eight to thirteen days. Guinea-pigs show practically no reaction following the first injection. Both react to a second injection. The reactions in man and the guinea-pig, however, differ both in severity and in kind. The relation, therefore, that our observations on the guinea-pig may have in its application to man must await further study. Of course, the fact that other animals beside man and guinea-pigs react to a second injection of horse serum would seem to indicate that we are dealing with one and the same reaction.

It has been shown that rabbits react after repeated injections, which has also been noted in the use of repeated injections of the serum in man.

#### THE RELATION OF SERUM ANAPHYLAXIS IN THE GUINEA-PIG TO SERUM THERAPY

Besredka and Steinhardt were the first to point out that the second injection may be given into the brain of guinea-pigs. When a small quantity of horse serum is injected into the brain of a sensitized guinea-pig the symptoms appear promptly and often with great violence, and death is a common result.

Besredka believes that intracerebral injections may be used as a measure of the toxicity of therapeutic serums. He states that, measured in this way, different serums show a wide gamut of toxicity, the fatal dose varying from  $\frac{1}{4}$  to  $\frac{1}{128}$  of a cubic centimeter. He believes that this toxicity resides in the serum and not in the cellular elements; further, that the serum of horses living under apparently the same conditions has about the same toxicity, individual variations being rare and of little importance. He concludes that, in a general way, all serums which incite in guinea-pigs grave anaphylactic phenomena in doses of 0.0625 to 0.05 c.c. and *a priori* above this amount should be considered toxic.

We doubt whether there is a relation between the toxicity of serums as tested on guinea-pigs in this way and their power to produce the serum disease or collapse or sudden death in man. It appears to us that in man the symptoms of the serum disease depend partly on the kind of serum and the amount used. The unfortunate accidents, such as collapse and sudden death, depend more on the sensitization of the individual than on the so-called toxicity of the serum used.

Fortunately, we were able to obtain two antidiphtheria serums which had been used in two cases followed by sudden death:

CASE 1.—Serum No. 2277. Reported by Dr. S. N. Wiley, Norristown, Pa., (*Jour. Am. Med. Assn.*, 1908, i, 137). Mr. E. W., aged 34 years, splendid physique, best of health. Prophylactic injection of 1,000 units antidiphtheric serum. Site of inoculation four inches above Poupart's ligament. Within two minutes had violent symptoms—anxious expression, itching, burning, labored breathing; lips, face and neck swollen and red; paralysis; convulsions. Died within five minutes of injection.

CASE 2.—Serum No. 2295. Reported by Dr. H. F. Gillette, Cuba, N. Y., (*Jour. Am. Med. Assn.*, 1908, i, 40). Mr. B., 52 years old. Had asthma and bronchial catarrh. Urine and heart normal. Rheumatic attack fifteen years ago. Coughed and raised plenty of sputum. Injection of 2,000 units antitoxin serum under left scapula. Prickling sensation in neck and chest, labored breathing, pulse regular and full. Seized with tonic spasm. Died within five minutes after injection.

From our experiments it is plain that the serums which do not produce untoward symptoms when injected into man are quite as toxic on sensitized guinea-pigs as the serums which have been followed by serious symptoms when injected into man. We believe that the difference lies in the susceptibility of the individual and not in the toxicity of the serum.

It has interested us very much to find that the above two cases, and also others that have come to our notice, were in asthmatics. In our first publication we suggested that the essential lesion of serum anaphylaxis is probably localized in the respiratory center, and the association of asthma and hypersusceptibility to horse serum in man would seem to lend weight to this hypothesis. The knowledge of the fact that the injection of horse serum into some asthmatics is attended with danger must be considered in the use of antitoxin.

#### HYPERSENSITIBILITY AND IMMUNITY PRODUCED BY BACTERIAL PROTEINS

We believe that the problem of hypersusceptibility has an important bearing on the question of immunity and hence we have expressed the opinion that "resistance to disease may largely be gained through a process of hypersusceptibility. Whether this increased susceptibility is an essential element or only one stage in the process of resistance to disease must now engage our attention." We can not escape the conviction that this phenomenon of hypersusceptibility has an important bearing on the prevention and cure of certain infectious processes. Our work on the hypersusceptibility produced by the bacterial proteins strengthens this belief, for our recent results prove that the phenomenon



of hypersusceptibility to certain proteid substances extracted from the bacterial cell is followed by a definite immunity against infection by the corresponding micro-organism.

Experimental study of the bacterial proteins is of the greatest importance on account of the practical uses to which results along this line may lead. The relation of these studies to the so-called endotoxins is evident.

Hypersusceptibility may easily be induced in guinea-pigs with protein extracts obtained from the bacterial cell. The first injection of most of the extracts used by us seems comparatively harmless to the animal. A second injection of the same extract shows, however, that profound physiologic changes have taken place. A definite period must elapse between the first and the second injection. The symptoms presented by the guinea-pigs as a result of the second injection resemble those caused by horse serum. The phenomenon induced by a second injection is followed (in certain cases) by an immunity to the corresponding infection.

These results strengthen our belief that the phenomenon of hypersusceptibility has a practical significance in the prevention and cure of certain infectious processes. It also gives a possible explanation of the period of incubation of some of the communicable diseases. Is it a coincidence that the period of incubation of a number of infectious diseases is about ten to fourteen days, which corresponds significantly with the time required to sensitize animals with a strange protein?

In certain infectious diseases with short periods of incubation, such as pneumonia, the crisis which commonly appears about the tenth day may find a somewhat similar explanation. It is evident that disease processes produced by soluble toxins, such as diphtheria and tetanus, do not belong to the category now under consideration.

The hypersusceptibility produced by the colon and typhoid bacilli was followed by a definite immunity to the corresponding infection. In case of anthrax, however, immunity does not follow hypersusceptibility to the anthrax protein. We are not dealing, therefore, with a general law applicable to all infections, but with certain limitations, as in the case of antitoxic immunity.

#### THE RELATION OF ANAPHYLAXIS TO THE TOXEMIAS OF PREGNANCY

The symptoms of puerperal eclampsia and the conditions under which it occurs suggest that anaphylaxis may explain some of the mystery of this state.

It occurred to us that either the blood or protein substance in solution from the fetus or the placenta may first sensitize the mother. A subsequent introduction into the system of the mother of a similar substance may explain the convulsions and the symptoms which occur in a certain class of the toxemias of pregnancy.

There seems to be a fair agreement that the placenta must be the source of the toxic material, especially as typical cases of eclampsia and pernicious vomiting have been observed in patients with hydatid mole in which cases, of course, toxic matter of fetal origin could be eliminated. Furthermore, eclampsia may appear after the fetus has been removed. Much attention was therefore given to the hypothesis elaborated about four years ago by Veit, Weichardt and others that, through the entrance of placental cells into the circulation of the mother, an intoxication was caused either by disintegration of the cells and the formation of toxic substances or in the development of anti-substances by the maternal organism.

In spite of much experimentation and discussion, however, no satisfactory conclusions have yet been reached concerning the validity of this hypothesis and Martin has secured some very valuable evidence that, at least in rabbits, entrance of their own placental elements into the circulation in large amounts does not cause any serious disturbance.

Along these lines we made a number of experiments to determine whether the fetal blood of the guinea-pig could sensitize the mother guinea-pig. We injected a number of female guinea-pigs, both pregnant and not pregnant, with fetal blood and, after an appropriate interval, gave them a second injection of the same material. All these experiments resulted negatively, which was anticipated from our previous studies upon the effect of homologous blood serums. This is in harmony with the clinical observations that the poisons causing the toxemias of pregnancy do not come from the fetus.

We made a series of experiments on female guinea-pigs with guinea-pig placental extracts. The placenta (almost at full term) was ground up and allowed to autolyze about an hour at room temperature and some of the resulting extract was injected subcutaneously into female guinea-pigs.

From our studies it was evident that the mother guinea-pig may be sensitized with the autolytic products of her own placenta. These experiments naturally suggest that there may be a certain relation between some cases of puerperal eclampsia and the phenomenon in the guinea-pig which we are studying. Further studies along this line are now being made.

## AN EXPLANATION OF THE PERIOD OF INCUBATION OF CERTAIN INFECTIONS

The only plausible explanation of the period of incubation of an infectious disease heretofore considered has been that it required a certain time for the infective principle to grow in sufficient amount in the body to produce symptoms. This view is not tenable in many cases. The period of incubation in many cases is independent of the amount of infection.

In view of the studies on anaphylaxis we now have a more likely explanation of the period of incubation in certain cases. If the body is sensitized by the foreign protein dissolved out of the infecting organism it would require a certain definite time before the poisonous effects are felt. This not only explains why a certain time must elapse between the introduction of the infection and the onset of the disease, but gives us our first clew to the constancy of the period of incubation of certain maladies.

## ANTIBODIES

We showed in our first publication in 1906 that the mechanism of anaphylaxis did not depend on an antibody free in the blood serum and body juices, as is the case in diphtheria and tetanus. In other words, this phenomenon is not simply a neutralization of a soluble poison by a soluble antipoison. There are antibodies other than free receptors which are readily demonstrable *in vitro* and *in vivo*. The definition of an antibody still lacks precision, and the action of these substances is not clearly understood. In this state of our knowledge it would be dogmatic to insist that the phenomenon of hypersusceptibility depends on the action of an antibody. The indications, however, seem to be that we are dealing with such an agent.

The anaphylactin readily demonstrable in the blood of a guinea-pig many months after the introduction of a minute fraction of a cubic centimeter of horse serum subcutaneously, can hardly be a portion or "rest" of the original minute amount of foreign protein injected. It seems probable that the introduction of the foreign protein stimulates or calls forth the production of anaphylactin, which flows free in the blood serum in relatively considerable amounts. There is evidence to indicate that anaphylactin is present in the blood serum in amounts greater than the amount of foreign protein originally introduced into the body.

We have shown that anaphylactin is present in the blood serum of immune guinea-pigs. This observation is very significant in this connection, for it indicates that the cells are protected despite the fact

that they are continually bathed with the serum containing the sensitizing principle. The readiest explanation of this form of cellular immunity is the conception of a neutralizing antibody.

The further fact that hypersusceptibility, and not immunity to anaphylaxis, is transmitted from mother to young is another indication that we are dealing with an antibody.

Vaughan, Lewis, Nicolle, Besredka and most others—except Gay and Southard—who have studied this phase of the question consider an antibody necessary to explain the intimate nature of the phenomenon.

#### RELATION OF ANAPHYLAXIS TO PROTEIN METABOLISM

It is interesting to note that Ehrlich's explanation of antitoxic immunity was based on a chemical conception of protein metabolism. Ehrlich's haptophore side-chains that seize the toxin molecule have the same or similar affinities as those that seize and combine with the protein food molecule.

Another great conception of immunity, developed by Metchnikoff, is also clearly associated with protein metabolism or cellular digestion.

We now have another conception of immunity in certain infections based on the action caused by the introduction of a foreign protein into the body. This view is also closely bound up with the subject of protein metabolism. It can not but excite our wonder that the chemistry of the body should be so delicately balanced that the introduction of 1/10,000,000 part of a gram of foreign protein should be able so profoundly to influence it as to result in serious symptoms when injected a second time.

The whole problem of protein metabolism seems to be an adjustment in the sense of a defense. The power to assimilate and use foreign proteins is not achieved without a certain amount of violence to the body. The relation between the fundamental facts of protein metabolism and the immunity to certain diseases becomes clearer in the light of observations upon anaphylaxis. Work on both these problems will throw light on the fundamental processes of each other.

#### RELATION OF ANAPHYLAXIS TO ENDOTOXINS

The fact that the great majority of bacteria do not produce soluble poisons such as diphtheria and tetanus has led to the belief that in such cases we are dealing with an "endotoxin." The endotoxin has long been regarded as a poisonous substance so intimately associated with the cell that it is not released until the microbic cell is broken up in the body. The inability to demonstrate these endotoxins has cast

a doubt on their existence and increased the mystery of their action. It now seems probable that the studies on anaphylaxis may throw light upon this question.

When bacteria grow in the body they are dissolved by lytic agencies and the foreign protein in the individual germ cells may sensitize the body and afterwards poison it. The bacterial proteins may not be poisonous in themselves in the sense of an "endotoxin." We have, in fact, shown that protein extracts of bacterial cells at the first injection may produce characteristic symptoms, and this reaction may be followed by an immunity to the corresponding infection.

#### THE RELATION OF ANAPHYLAXIS TO TUBERCULOSIS

The tuberculin reaction is one of the best known instances of anaphylaxis. Following a local infection with the tubercle bacillus the tissues generally become hypersusceptible to tuberculin. We have shown that a local hypersusceptibility may be produced by the direct application of tuberculin to certain tissues (conjunctiva). The same has been demonstrated for the skin, and is probably true of other tissues. This hypersusceptibility of the tissues immediately surrounding a tuberculous focus helps to encapsulate and limit the process. Should a tubercle bacillus lodge in or on a tissue in a state of tuberculin anaphylaxis the result is that all of Nature's protecting agencies are quickly concentrated on the point where they are most needed. We conceive that this active power of reacting quickly is not only an important factor in individual prophylaxis against tuberculosis, but it is one of the important agencies which prevent the spread of the disease after it has obtained a lodgment in the body.

The normal individual does not react to tuberculin. The tuberculous individual reacts promptly, except in the final stage of the disease. The difference between the normal individual and the individual in the final stage of tuberculosis is that the former has not had his anaphylactic powers developed while the latter has had them developed and exhausted. A tuberculous individual in whom the specific power of hypersusceptibility to the poisons of the tubercle bacillus is broken down presents little or no resistance against the advance of the infection.

We may adduce a practical lesson from this: When tuberculin is used in large or too oft-repeated doses there is a tendency to break down or to exhaust the useful and beneficial hypersusceptible state of the tissues. In accordance with this line of reasoning, therefore, tuberculin would be of benefit in tuberculosis only when used in such

a way as to develop and not diminish the power of anaphylaxis of the tissues. This explanation has been borne out in the use of tuberculin.

While all of the views expressed here are based on experimental data, our interpretations of them may not all stand the test of time. It is evident, however, that studies on the subject of anaphylaxis give us a broader and deeper insight into some of the difficult and abstruse problems connected with both the recurrence of and the resistance to disease. The subject has proved a fruitful field for research. It has more than an academic interest. There is hope that a final solution of the mechanism of anaphylaxis will have a practical application in the treatment and prevention of a number of diseased states.

#### BIBLIOGRAPHY

1. Albrecht: Immunisierung gegen Heufieber durch Antitoxin und die beim Gebrauche des letzteren beobachteten Fälle von Anaphylaxie. *Med. Klin., Berl.*, 1908, No. 18.
2. Anderson (John F.): Transmission of resistance to diphtheria toxin by the female guinea-pig to her young. *Jour. Med. Research*, 1906, xv, 241.
3. Anderson (John F.): Simultaneous transmission of resistance to diphtheria toxin and hypersusceptibility to horse serum by the female guinea-pig to her young. *Jour. Med. Research*, 1906, xv, 259.
4. Anderson (John F.): I.—Maternal transmission of immunity to diphtheria toxin. II.—Maternal transmission of immunity to diphtheria toxin and hypersusceptibility to horse serum in the same animal. *Bulletin 30, Hyg. Lab. U. S. P. H. and M.-H. S.*, 1906.
5. Anderson (John F.): The antiseptic and germicidal properties of solutions of formaldehyd and their action on toxins. *Bull. 39, Hyg. Lab. U. S. P. H. and M.-H. S.*, July, 1907, 48 p.
6. Anderson (John F.); and Rosenau (M. J.): Further studies on anaphylaxis. *Jour. Med. Research*, 1908, xix, 37-66.
7. Arloing (S.): Cited by von Pirquet in *Allergie, Ergebn. inn. Med. u. Kinderh.*, i, 1908.
8. Arthus (M.): Injections répétées de sérum de cheval chez le lapin. *Compt. rend. Soc. biol., Paris*, 1903, lv, 20.
9. Arthus (Maurice): Injections répétées de sérum de cheval chez le lapin. *Compt. rend. Soc. biol., Paris*, 1903, lv, 817.
10. Bail: Ueberempfindlichkeit bei tuberkulösen Tieren. *Wien. klin. Wchnschr.*, 1904, p. 30.
11. Bail: Der akute Tod von Meerschwein an Tuberkulose. *Wiener klin. Wchnschr.*, 1905, p. 15.
12. Banzhaf (Edwin J.), and Famulener (L. W.): A note on anaphylaxis. *Proc. Soc. Exper. Biol. and Med.*, 1908, v, 62.
13. Beclère (A.), Chambon, and Menard: Etude expérimentelle des accidents post-sérothérapiques. *Ann. de l'Inst. Pasteur*, 1896, x, 567.
14. Belfanti and Carbone: Produzione di sostanze tossiche nel siero di animali inoculati con sangue eterogeneo. *Gior. d. r. Accad. di med., Torino*, 1898.
15. Besredka (A.): Toxicité des sérums thérapeutiques, sa variabilité et son dosage. *Ann. de l'Inst. Pasteur, Paris*, 1907, xxi, 777.
16. Besredka (A.): Comment peut-on combattre l'anaphylaxie? *Ann. de l'Inst. Pasteur, Paris*, 1907, xxi, 950.

17. Besredka (A.): De la toxicité des sérums thérapeutiques et du moyen de la doser. *Compt. rend. Soc. de biol.*, 1907, lxii, 477.
18. Besredka (A.): Comment empêcher l'anaphylaxie? *Compt. rend. Soc. de biol.*, Paris, 1907, lxii, 1053.
19. Besredka (A.): Du mécanisme de l'anaphylaxie vis-à-vis du sérum de cheval. Note préliminaire. *Compt. rend. Soc. de biol.*, Paris, 1907, lxiii, 294-296.
20. Besredka (A.): De l'anaphylaxie lactique. *Compt. rend. Soc. de biol.*, Paris, 1908, lxiv, 888-889.
21. Besredka (A.): Du mécanisme de l'anaphylaxie vis-à-vis du sérum de cheval. *Ann. de l'Inst. Pasteur*, Paris, 1908, xxii, 496-508.
22. Besredka (A.) and Steinhardt (Edna): De l'anaphylaxie et de l'anti-anaphylaxie vis-à-vis du sérum de cheval. *Ann. de l'Inst. Pasteur*, Paris, 1907, xxi, 117.
23. Besredka (A.) and Steinhardt (Edna): Du mécanisme de l'anti-anaphylaxie. *Ann. de l'Inst. Pasteur*, Paris, 1907, xxi, 384.
- 23a. Besredka (A.): De la vaccination antianaphylactique. *Comp. Rend. Soc. Biol.*, Par., 1908, lxv, 478.
24. Bienenfeld (B.): Die Leukoeyten in der Serumkrankheit. *Mitt. d. Gesellsch. f. inn. Med. u. Kinderh. in Wien*, 1907, vi, 55.
25. Bienenfeld (Bianca): Das Verhalten der Leukozyten bei der Serumkrankheit. *Jahrb. f. Kinderh. u. phys. Erziehung*, 1907, lxv, 174.
26. Bier (A.): Beeinflussung bösartiger Geschwülste durch Einspritzung von artfremdem Blut. *Deutsch. med. Wchnschr.*, 1907, xxxiii, 1162.
27. Blain (Alexander W.): Urticaria following the second administration of diphtheria antitoxin. *Med. Rec.*, 1908, lxxiii, 940.
28. Bligh (W.): Hypersensitization to antidiphtherial serum. *Brit. Med. Jour.*, 1908, i, 501.
29. Boone (E. L.): Sudden death following the use of diphtheria antitoxin. *Jour. Am. Med. Assn.*, 1908, l, 453.
30. Brieger: Weitere Erfahrungen über Bakteriengifte. *Ztschr. f. Hyg.*, 1895, 101.
31. Bruch (A.): Accidents très graves consécutifs à l'administration préventive de sérum antidiphthérique chez un malade ayant reçu sans inconvénient huit ans auparavant une injection de sérum. *Arch. de l'Inst. Pasteur de Tunis*, 1908, No. 2, pp. 81-84.
32. Buttersack: Immunität und Heilung im Lichte der Physiologie und Biologie. *Virchow's Arch. f. path. Anat.*, 1895, cxlii, 248.
33. Cabannes (E.): Recherches au sujet de la toxicité des sérums hétérogènes. *Compt. rend. Soc. biol.*, Paris, 1907, lxii, 809.
34. Cheney (Henry W.): The serum disease. *Illinois Med. Jour.*, 1907, xii, 248-253.
35. Coea (Arthur F.): The cause of sudden death following the intravenous injection of the blood corpuscles of foreign species. *Univ. Penn. Med. Bull.*, 1908, xxi, 243.
36. Courmont (Paul): Etudes sur les substances solubles prédisposantes à l'action pathogène de leurs microbes producteurs. *Rev. de méd.*, 1891, x.
37. Courmont (Paul): Sur la toxicité à la clinique du Prof. Bondet et au laboratoire de M. Arloing. *Arch. internat. de pharmacodyn. et therap.*, 1900, vii, 281.
38. Courmont (Paul): De l'anaphylaxie avec les liquides de pleurésies tuberculeuses. (Essai d'explication de l'anaphylaxie.) *Prov. méd.*, June 22, 1907.
39. Currie (J. R.): On the supersensitization of persons suffering from diphtheria by repeated injections of horse serum. *Jour. Hyg.*, 1907, vii, 35.

40. Currie (J. R.): Abnormal reactions to horse serum in the serum treatment of cerebrospinal fever. *Jour. Hyg.*, 1908, viii, 457.
41. Dallera: Considerazioni e casi clinici di trasfusione del sangue. *Morgagni*, 1874, vii.
42. Delnc and Hamburger (F.): Experimentelle Untersuchungen über die Folgen parenteraler Einverleibung von Pferdeserum. *Wien. klin. Wchnschr.*, 1904.
43. Detre-Deutsch: Superinfektion und Primäraffekt. *Wien. klin. Wchnschr.*, 1904.
44. Detre (L.): [The serum disease.] *Bör-esbyakört*, Budapest, 1907, p. 3-6; 25-28.
45. DeWaele (H.): La réaction à la tuberculine. *Ann. Soc. de méd. de Gand.*, 1906, lxxiv, 84.
46. DeWaele (H.): Etude sur l'immunité conférée par la méthode des saes de cellulose et sur les produits microbiens dialysants. *Centralbl. f. Bakt.*, 1906, xlii, 636, 760.
47. DeWaele (H.): Contribution à l'étude de l'anaphylaxie. *Bull. Acad. roy. de méd. de Belge*, 1907, p. 715.
48. Doerr (R.): Ueber Anaphylaxie. *Wien. klin. Wchnschr.*, 1908, xxi, 415.
49. Doerr (R.) and Baubitschek (H.): Toxin und anaphylaxirende Substanz des Heilserums. *Berl. klin. Wchnschr.*, 1908, xxxiii, 1525.
50. Dogge (Charles A.): A case of sudden death after injection of anti-toxin. *Pediatrics*, 1896, ii, 12.
51. Francioni: La malattia da siero. *La Sperimentale*. 1904, 767.
52. Francioni: Perdita dell'immunità passiva in seguito alla malattia da siero nella difterite. *Riv. di clin. ped.*, 1907.
53. Friedemann (U.): Ueber passive Ueberempfindlichkeit. *München. med. Wchnschr.*, 1907, 2414.
54. Friedemann (U.) and Isaac (S.): Ueber Eiweissimmunität und Eiweissstoffwechsel. *Ztschr. f. exper. Path. u. Therap.*, 1905 & 1906.
55. Friedman (Ulrich) and Isaacs (S.): Weitere Untersuchungen über den parenteralen Eiweissstoffwechsel, Immunität und Ueberempfindlichkeit. *Ztschr. f. exper. Path. u. Therap.*, 1907, iv, 830.
56. Gabel (Wilhelm): Zwei Fälle von Serumatosi (Serumkrankheiten). *Centralbl. f. Kinderh.*, 1907, xii, 421.
57. Gay (Frederick P.) and Adler (Herman M.): The chemical separation of the sensitizing fraction (anaphylactin) from horse serum. *Jour. Med. Research*, 1908, xviii, 433.
58. Gay (F. P.) and Southard (E. E.): Serum anaphylaxis in the guinea-pig. *Jour. Med. Research*, 1907, xvi, 143.
59. Gay (Frederick P.) and Southard (Elmer E.): The mechanism of serum anaphylaxis and intoxication in the guinea-pig. *Jour. Med. Research*, 1908, xviii, 407.
60. Gay (Frederick P.) and Southard (Elmer E.): Recurrent anaphylaxis and repeated intoxication in guinea-pigs by means of horse serum. *Jour. Med. Research*, 1908, xix, 1.
61. Gay (Frederick P.) and Southard (Elmer E.): The relative specificity of anaphylaxis. *Jour. Med. Research*, 1908, xix, 5.
62. Gay (Frederick P.) and Southard (Elmer E.): The localization of cell and tissue anaphylaxis in the guinea-pig, with observations on the cause of death in serum intoxication. *Jour. Med. Research*, 1908, xix, 17.
63. Gillette (Herbert F.): Diphtheria antitoxin in bronchial asthma. *Jour. Am. Med. Assn.*, 1908, i, 40.



64. Goodall (E. W.): The supersensitization of persons by horse serum. *Jour. Hyg.*, 1907, vii, 607.
65. Grunbaum (Albert S.): Supersensitization to alien serum. *Jour. Hyg.*, 1908, viii, 9-13.
66. Hamburger (F.): Zur Frage der Immunitätsbildung gegen Eiweiss. *Wien. klin. Wchnschr.*, 1902.
67. Hamburger (F.): Arteigenheit und Assimilation. Vienna, Deuticke, 1904.
68. Hamburger (F.): Ueber Antitoxin und Eiweiss; experimentelle Studie. *München. med. Wchnschr.*, 1907, liv, 254.
69. Hamburger (F.) and Moro (E.): Ueber die biologisch nachweisbaren Veränderungen des menschlichen Blutes nach Seruminjektion. *Wien. klin. Wchnschr.*, 1903.
70. Hamburger (F.) and von Reuss: Die Folgen parenteraler Infektion von verschiedenen genuinen Eiweisskörpern. *Wien. klin. Wchnschr.*, 1904.
71. Hamburger (F.) and von Reuss: Ueber die Wirkung artfremden genuinen Eiweisses auf die Leukoeyten. *Ztschr. f. Biol.*, 1905, xlvii, 24.
72. Hamman (Louis): The use and the value of tuberculin in the diagnosis of pulmonary tuberculosis. *The Archives Int. Med.*, 1908, i, 443.
73. Hartung: Die Serumexantheme bei Diphtherie. *Jahrb. f. Kinderh.*, 1896, xlii, 72.
74. Heilner (Ernst): Ueber die Wirkung grosser Mengen artfremden Blutserums in Tierkörper nach Zufuhr per Os und subkutan. *Ztschr. f. Biol.*, 1907, i, 26.
75. Heilner (E.): Ueber die Wirkung künstlich erzeugter physikalischer (osmotischer) Vorgänge im Tierkörper auf den Gesamtstoffumsatz mit Berücksichtigung der Frage von der Überempfindlichkeit. *Ztschr. f. Biol.*, 1907, i.
76. Heim (P.) and John (K.): Allergie und Tuberkulinfiltratproben nach von Pirquet-Detre. *Wien. klin. Wchnschr.*, 1908, No. 8.
77. Hericourt (J.) and Richey (C.): Effets lointains des injections de sérum d'anguille. *Compt. rend. Soc. biol., Paris*, Feb. 4, 1898, p. 137.
78. Johannessen (Axel): Ueber Injektionen mit antidiphtherischem Serum und reinem Pferdserum. *Deutsch. med. Wchnschr.*, 1895, xxi, 855.
79. Kassowitz: Metabolismus und Immunität. *Wien. med. Wchnschr.*, 1906.
- 79a. Kinyoun (J. J.): The toxic effects of horse serum. *Science*, 1907, xxv, 810-811.
80. Kladnitski (N. N.): [Three cases of serum disease.] *Vrach. gaz., St. Petersburg*, 1906, xiii, 1353.
81. Klotz (Oscar): Sudden death following serum inoculations. *Montreal Med. Jour.*, 1907, xxxvi, 615-618.
82. Knorr: Experimentelle Untersuchungen über die Grenzen der Heilungsmöglichkeit des Tetanus. *Habilitationsschrift, Marbourg*, 1895, 31 pp. 8 pls., 8vo.
83. Krauss (V. R.) and Doerr (R.): Ueber Anaphylaxie. *Centralbl. f. Bakteriologie*, 1908, xlii, 36.
84. Lehdorff: Serumkrankheit nach wiederholten Seruminjektionen. *Monatsschr. f. Kinderh.*, 1906, iv.
85. Lemaire (Henri): Note sur quelques effets d'une injection de sérum antidiphthérique chez le lapin. *Compt. rend. Soc. biol., Paris*, 1906, lx, 632.
86. Lemaire (H.): Recherches cliniques et expérimentales sur les accidents sérotoxiques. *Thèse de Paris*, 1906.
87. Lemaire (Henri): Recherches cliniques et expérimentales sur les accidents séro-toxiques. *Paris*, 1907, roy. 8vo, 160 p.
88. Lewis (Paul A.): The induced susceptibility of the guinea-pig to the toxic action of the blood serum of the horse. *Jour. Exper. Med.*, 1908, x, 1-29.

89. Lewis (Paul A.): Further observations on anaphylaxis to horse serum. *Jour. Exper. Med.*, 1908, x, 608-617.
90. Löwenstein and Rappaport (E.): Ueber den Mechanismus der Tuberkulininität. *Ztschr. f. Tuberk.*, 1904, vi, 566.
91. Maec (Lewis Sayre): The reaction of anaphylaxis. *California State Jour. Med.*, 1908, vi, 174-176.
92. Magendie: *Vorlesungen über das Blut*, German translation by Krupp, 1839; edited by Ehrlich: *Collected studies on immunity*, transl. by Charles Bolduan. New York, John Wiley, 1906, p. 332.
93. Marfan and Lemaire (H.): Contribution à l'étude des accidents sérotoxiques. L'érythème marginé aberrant. *Rev. mens. d. mal. de l'enf.*, January, 1907.
94. Marfan and LePlay: Recherches sur la pathogénie des accidents sérotherapiques. *Soc. méd. d. hop.*, March 24 and May 19, 1905.
95. McClintock and King: The oral administration of antitoxins for prevention of diphtheria, tetanus, and possibly sepsis, with some observations on the influence of certain drugs in preventing digestion and promoting absorption from the alimentary canal. *Jour. Infect. Dis.*, 1906, iii, 700-720.
96. Moro (E.): Tuberculin reaction and the nervous system. *München. med. Wchnschr.*, 1908, iv, 2025.
97. Much (H.): Ueber die antitoxische Funktion und Eiweiss. *München. med. Wchnschr.*, 1907, liv, 2589.
98. Netter (Arnold): Efficacité de l'ingestion de chlorure de calcium comme moyen preventif des éruptions consécutives aux injections de sérums. *Compt. rend. Soc. de biol.*, Paris, 1906, lx, 279.
99. Netter (Arnold): Influence des quantités de sérum injectées et du nombre des injections sur les éruptions sériques. *Compt. rend. Soc. de biol.*, Paris, 1906, lx, 281.
100. Nicolle (Maurice): Contribution à l'étude du "phénomène d'Arthus." *Ann. de l'Inst. Pasteur*, Paris, 1907, xxi, 128.
101. Nicolle (M.): Une conception générale des anticorps et de leurs effets. *Compt. rend. Soc. de biol.*, Paris, 1907, lxiii, 77.
102. Nicolle (M.) and Pozerski (E.): Les anticorps des toxines solubles; Nicolle (M.) and Abt: Les anticorps des albuminoides et des cellules. Nicolle (M.): Les anticorps normaux. *Ann. de l'Inst. Pasteur*, 1908, xxii.
103. Ohlmacher (A. P.): The reaction of hypersusceptibility as produced by bacterial inoculations. *Jour. Med. Research*, July, 1908, xix, 113.
104. Otto (R.): Das Theobald Smith'sche phänomen der Serum-Ueberempfindlichkeit. *Von Leuthold Gedenkschrift*, 1905, i.
105. Otto (R.): Zur Frage Serum-Ueberempfindlichkeit. *München. med. Wchnschr.*, 1907, liv, 1665.
106. Otto (R.): Ueber Anaphylaxie und Serumkrankheit, im besonderen über experimentelle Serum-Ueberempfindlichkeit. *Handbuch der patho. Mikroorganismen*, by Kolle and Wassermann, 1908, ii, 255.
107. Park (Wm. H.): The effects on man of injections of horse serum; serum sickness. *Harvey Lecture*, Philadelphia and London, 1906, p. 107.
108. Pfeiffer (Hermann): Ueber die nekrotisierende Wirkung normaler Serum. *Wien. klin. Wchnschr.*, 1905, xviii, p. 465.
109. Portier and Richet (C.): De l'action anaphylactique de certains venins. *Compt. rend. Soc. biol.*, Paris, 1902, lxiv, 170.
110. Pozerski (E.): Anaphylaxie du cobaye pour la papaine. *Compt. rend. Soc. de biol.*, Paris, 1908, lxiv, 631-632.
111. Preisich (K.) and Heim (P.): Ueber das Wesen der Tuberkulinreaktion. *Centralbl. f. Bakteriöl.*, 1902, xxxi, 681.

112. Quigley (James Knight): Collapse after the use of diphtheria anti-toxin. *Jour. Am. Med. Assn.*, 1908, 1, 768.
113. Remlinger (P.): Absence d'anaphylaxie au cours des injections sous-cutanées de virus rabique et de serum antirabique. *Compt. rend. Soc. de biol.*, Paris, 1906, lxi, 475-476.
114. Remlinger (P.): Contribution a l'étude du phénomène d'anaphylaxie. *Compt. rend. Soc. de biol.*, Paris, 1907, lxii, 23-25.
115. Remlinger (P.): Absence d'anaphylaxie à la suite d'injections sous-cutanées de substance nerveuse. *Compt. rend. Soc. de biol.*, Paris, 1908, lxiv, 641-645.
116. Richet (C.): De l'anaphylaxie, ou sensibilité croissante des organismes à des doses successives de poison. *Arch. de fisiol.*, 1904, i, 129.
117. Richet (C.): De l'action de la congestine (virus des actines) sur les lapins et des effets anaphylactiques. *Compt. rend. Soc. biol.*, Paris, 1905, lviii, 109.
118. Richet (C.): De l'anaphylactique après injections des congestine, chez le chien. *Compt. rend. Soc. biol.*, Paris, 1905, lviii, 112.
119. Richet (C.): Anaphylaxie par injections d'apomorphine. *Compt. rend. Soc. biol.*, 1905, lviii, 955.
120. Richet (C.): Anaphylaxie par la mytilo-congestine. *Compt. rend. Soc. de biol.*, Paris, 1907, lxii, 358-368.
121. Richet (C.): Mesure de l'anaphylaxie par la dose émétisante. *Compt. rend. Soc. biol.*, Paris, 1907, lxii, 643.
122. Richet (Charles): De l'anaphylaxie en général et de l'anaphylaxie par la mytilo-congestine en particulier. *Ann. de l'Inst. Pasteur*, Paris, 1907, xxi, 497.
123. Richet (C.): De l'anaphylaxie et des toxogénines. *Ann. de l'Inst. Pasteur*, Paris, 1908, xxii, 465.
124. Richet (Charles): De la substance anaphylactisante du toxogénine. *Compt. rend. Soc. de biol.*, Paris, 1908, lxiv, 846-848.
125. Richet (C.): Note sur l'anaphylaxie. Des propriétés différentes dissociables par la chaleur d'une substance toxique. *Compt. rend. Soc. biol.*, Paris, 1908, lxxv, 404.
126. Richet (C.): Note sur l'anaphylaxie. *Comp. Rend. Soc. Biol.*, 1908, lxxv, 404.
127. Rosenau (M. J.) and Anderson (John F.): A study of the cause of sudden death following the injection of horse serum. *Bull. 29 Hyg. Lab. U. S. P. H. and M.-H. S.*, 1906.
128. Rosenau (M. J.) and Anderson (John F.): A new toxic action of horse serum. *Jour. Med. Research*, 1906, xv, 179.
129. Rosenau (M. J.) and Anderson (John F.): Hypersusceptibility. *Jour. Am. Med. Assn.*, 1906, xlvii, 1007.
130. Rosenau (M. J.) and Anderson (John F.): Studies on hypersusceptibility and immunity. *Bull. 36 Hyg. Lab. U. S. P. H. and M.-H. S.*, April, 1907.
131. Rosenau (M. J.) and Anderson (John F.): Further studies on hypersusceptibility and immunity. *Jour. Med. Research*, 1907, xvi, 381.
132. Rosenau (M. J.) and Anderson (John F.): The specific nature of anaphylaxis. *Jour. Infect. Dis.*, 1907, iv, 552.
133. Rosenau (M. J.) and Anderson (John F.): Anaphylaxis. Reference handbook of medical sciences, 1908, viii, 353.
134. Rosenau (M. J.) and Anderson (John F.): A review of anaphylaxis with especial reference to immunity. *Jour. Infect. Dis.*, 1908, v, 85.
135. Rosenau (M. J.) and Anderson (John F.): The relation of anaphylaxis to the toxemias of pregnancy. *Tr. Assn. Am. Phys.*, 1908, xxiii.

136. Rosenau (M. J.) and Anderson (John F.): Further studies on phylaxis. Bull. 45 Hyg. Lab. U. S. P. H. and M.-H. S., June, 1908.
137. Rosenhaupt (H.): Klinischer Beiträge zur Serumkrankheit. Münch. med. Wehnschr., 1905, lii, 2019.
138. Rovere: Sur la présence de précipitines dans le sang de sujets atteints d'accidents consécutifs à des injections de sérum antidiphthérique. Arch. gén. de méd., 1906, vi.
139. Saeli: Sulle fine alterazioni di struttura degli organi per injectione di siero di sangue eterogene. Rif. med., 1905.
140. Salge: Einige Bemerkungen zu dem Thema "Arteigene und fremdes Eiweiss" in bezug auf die Säulingsernährung. Monatsschr. f. Kinderheilk., August, 1906.
141. Saward: Syncope occurring after injection of antitoxin in cases of diphtheria. Brit. Med. Jour., 1902, i, 1025.
142. Schick (B.): Kutan-Reaktion bei Impfung mit Diphtherietoxin. München. med. Wehnschr., 1908, lv, 504.
143. Schofield (Alfred T.): A case of egg poisoning. Lancet, London, 1908, clxxiv, 716.
144. Shibayama: Ueber die Wirkung der bakteriologischen Heilsera bei wiederholten Injektionen. Centralbl. f. Bakteriol., 1906, xli, 571.
145. Stadelmann and Wolff-Eisner: Ueber Typhus und Kolisepsis und über Typhus als Endotoxin-Krankheit. München. med. Wehnschr., 1907, liv, 1161, 1237.
146. Thorne (R. Thorne): Hypersensitiveness to antidiphtheric serum. Brit. Med. Jour., 1908, i, 147.
147. Torkomian: Maladie du sérum. Gaz. méd. d'orient, 1906, li, 162.
148. Uhlenhuth: Zur Kenntniss der giftigen Eigenschaften des Blutserums. Ztschr. f. Hyg., 1897, xxvi, 384.
149. Vasconcellos (F.): Anaphylaxia. Two brochures of 9 and 20 pages from the Institut de Manguinhos. Rio de Janeiro, 1907.
150. Vaughan (V. C.): Discussion of Rosenau and Anderson's paper on Hypersusceptibility. Jour. Am. Med. Assn., 1906, xlvii, 1009.
151. Vaughan (Victor C.): Hypersusceptibility and immunity. Science, 1908, xxvii, 644.
152. Vaughan (Victor C.) and Wheeler (Sybil May): The effects of egg-white and its split products on animals. A study of susceptibility and immunity. Tr. Assn. Am. Phys., 1907, xxii, 268. Jour. Infec. Dis., 1907, iv, 476.
153. Von Behring (E.) and Kitashima (S.): Ueber Verminderung und Steigerung der erworbenen Giftempfindlichkeit. Berl. klin. Wehnschr., 1901, 157.
154. Von Pirquet (C.): Zur Theorie der Infektionskrankheiten. Vorläufige Mitteilung, April 2, 1903. Veröffentl. d. k. Akad. d. Wissensch. Wien, Feb. 13, 1908.
155. Von Pirquet (C.): Allergie. München. med. Wehnschr., 1906, No. 30.
156. Von Pirquet (C.): Ist die Vakzinale Frühreaktion spezifisch? Wiener klin. Woch., 1906, xix, No. 47.
157. Von Pirquet (C.): Die frühzeitige Reaktion bei der Schutzpockenimpfung. Wien. klin. Wehnschr., 1906, xix, 28.
158. Von Pirquet (C.): Die cutäne Tuberkulinprobe. Med. Klin., 1907. Verhandl. d. Gesellsch. f. Kinderh., 1907.
159. Von Pirquet (C.): Tuberkulindiagnose durch cutäne Impfung. Berl. klin. Wehnschr., 1907.
160. Von Pirquet (C.): Der diagnostische Wert der cutänen Tuberkulinreaktion auf Grund von 100 Sektionen. Wien. klin. Wehnschr., 1907.
161. Von Pirquet (C.): Die Allergieprobe zur Diagnose der Tuberkulose im Kindesalter. Wien. med. Wehnschr., 1907, No. 28.

162. Von Pirquet (C.): Allergie-Diagnostik. Therap. Monatsh, November, 1907.
163. Von Pirquet (C.): Klinische Studien über Vakzination und vakzinale Allergie. Leipzig, Franz Deuticke, 1907, 194 p.
164. Von Pirquet (C.): Cutäne und conjunctivale Tuberkulinreaktion. Handbueh Kraus & Levaditi, 1908.
165. Von Pirquet (C.): Zur Diskussion über die cutäne und conjunctivale Tuberkulinreaktion. Berl. klin. Woch., 1908, No. 9.
166. Von Pirquet (C.): Allergie. Ergebn d. inn. Med. u. Kinderh., Julius Springer, Berlin, 1908.
167. Von Pirquet (C.) and Schick (B.): Zur Theorie der Inkubationszeit. (Vorläufige Mitteilung.) Wien. klin. Wchnsehr., 1903, No. 45.
168. Von Pirquet (C.) and Schick (B.): Zur Theorie der Inkubationszeit. Wien. klin. Wchnsehr., 1903, No. 45.
169. Von Pirquet (C.) and Schick (B.): Zur Frage der Aggressins. Wien. klin. Wchnsehr., 1905.
170. Von Pirquet (C.) and Schick (B.): Die Serumkrankheit. Leipsic, Franz Deuticke, 1905, 144 pp.
171. Wassermann (A.): Wesen der Infektion. Kolle & Wassermann's Handbueh der pathogenescher Mikroorgamsmen, 1903, i, 223.
172. Wassermann (A.) and Bruek (C.): Experimentelle Studien über Wirkung von Tuberkelbacillenpräparaten auf den tuberkulös erkrankten Organismus. Deutsch. med. Wchnsehr., 1906, xxxii, 449.
173. Wassermann (A.) and Citron (J.): Die lokale Immunität der Gewebe und ihre praktische Wichtigkeit. Deutsch. med. Wchnsehr., 1905, xxxi, 573.
174. Waterhouse (Rupert): Hypersensitization to antidiphtherial serum. Brit. Med. Jour., 1908, i, 925-926.
175. Weil-Halle (B.) and Lemaire (H.): Quelques conditions de l'anaphylaxie sérique passive chez le lapin et le cobaye. Compt. rend. Soc. de biol., Paris, 1907, lxiii, 748-750.
176. Weil-Halle und Lemaire (Henri): L'anaphylaxie passive du cobaye pour le serum de cheval. Compt. rend. Soc. de biol., Paris, 1908, lxx, 141-142.
177. Wells (H. Gideon): The nature of the poisonous element of proteins that is concerned in the reaction of hypersensitization. Jour. Am. Med. Assn., 1908, 1, 527-528.
178. Wells (H. Gideon): Studies on the chemistry of anaphylaxis. Jour. Infect. Dis., 1908, v, 449-483.
179. Wolff-Eisner (A.): Ueber Grundgesetze der Immunität. Ztsehr. f. Bakteriöl., 1904. Berl. klin. Wchnsehr., 1904, xli, 1105, 1131, 1156, 1273.
180. Wolff-Eisner (A.): Ueber die Urticaria vom Standpunkte der neuen Erfahrungen. Dermat. Zentralbl., 1906, x.
181. Wolff-Eisner (A.): Das Heufieber, sein Wesen und seine Bedeutung. München, J. F. Lehmann, 1906.
182. Wolff-Eisner (A.): Die Endotoxinlehre. München med. Wchnsehr., 1906, liii, 217.
183. Wolff-Eisner (Alfred): Ueber Eiweissimmunität und ihre Beziehungen zur Serumkrankheit. Centralbl. f. Bakteriöl., 1906, xl, 378.
184. Wolff-Eisner (A.): Typhustoxin, Typhusantitoxin und Typhusendotoxin. Die Beziehungen zwischen Ueberempfindlichkeit und Immunität. Berl. klin. Wchnsehr., 1907, xlv.

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